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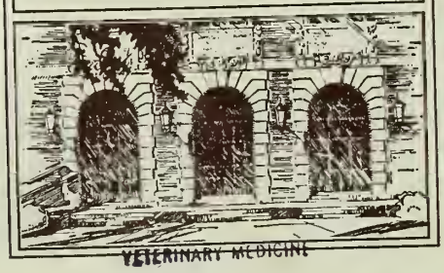

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CARCINOGENESIS ABSTRACTS

National Cancer Institute

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CARCINOGENESIS ABSTRACTS

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National Cancer Institute

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PREFACE

Vet Med

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For ournals not covered by *Index Medicus*, the abbreviations found in *Chemical Abstracts Service Source Index*, 907-1974 Cumulative, are used. New journals are verified in *New Serial Titles* and abbreviated according o *International Standard ISO 833*. An asterisk indicates the author to address (other than the primary) in equesting reprints.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	Ind.	Indonesian
Ara.	Arabic	Ita.	Italian
Bul.	Bulgarian	Jpn.	Japanese
Chi.	Chinese	Kor.	Korean
Cro.	Croation	Lav.	Latvian
Cze.	Czech	Lit.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
Eng.	English	Por.	Portuguese
Est.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fle.	Flemish	Ser.	Serbo-Croatian
Fre.	French	Slo.	Slovak
Geo.	Georgian	Spa.	Spanish
Ger.	German	Swe.	Swedish
Gre.	Greek	Tha.	Thai
Heb.	Hebrew	Tur.	Turkish
Hun.	Hungarian	Ukr.	Ukrainian
Ice.	Icelandic	Vie.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

A	angstrom(s)
ACTH	adrenocorticotropic hormone
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
BCG	Bacillus Calmette Guerin
bid	twice daily
C	degrees centigrade
cal	calorie(s)
kcal	kilocalorie(s)
cc	cubic centimeter(s)
Ci	curie(s)
mCi	millicurie(s)
μCi	microcurie(s)
cm	centimeter(s)
CNS	central nervous system
cpm	counts per minute
dl	deciliter(s)
ml	milliliter(s)
μl	microliter(s)
DNA	deoxyribonucleic acid
ED_{50}	median effective dose
EDTA	ethylenediamine tetraacetic acid
ESR	erythrocyte sedimentation rate
g	gram(s)
kg	kilogram(s)
mg	milligram(s)
μg	microgram(s)
Hb	hemoglobin
hr	hour(s)
ia	intra-arterial
ic	intracerebral
icav	intracavitary
id	intradermal
ILS	increased life span
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratumorous
IU	International Unit
iv	intravenous
K_m	Michaelis constant
LD	lethal dose
M	molar
mM	millimolar
μM	micromolar
mOsm	milliosmolar
mEq	milliequivalents
min	minute(s)
mo	month(s)
MTD	maximum tolerated dose
N	normal concentration
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotidephosphate
NADPH	reduced nicotinamide adenine dinucleotide-phosphate
ng	nanogram(s) (10^{-9})
od	once daily
Pa	ambient pressure
PAS	periodic acid-Schiff
pg	picogram(s) (10^{-12})
pgEq	picogram equivalent
po	orally
ppb	parts per billion
ppm	parts per million
qid	four times daily
qod	every other day
QO_2	oxygen quotient
R	roentgen(s)
RBC	red blood cells (erythrocytes)
RNA	ribonucleic acid
sc	subcutaneous
sec	second(s)
SGOT	serum glutamic-oxalacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SRBS	sheep red blood cells
TCD	tissue culture dose
TCD_{50}	median tissue culture dose
tid	three times daily
U	unit(s)
mU	milliunit(s)
UV	ultraviolet
vol	volume
WBC	white blood cells (leukocytes)
wk	week(s)

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2401 PATULIN: A MYCOTOXIN OF POTENTIAL CONCERN IN FOODS. (Eng.) Stott, W. T. (Dept. Food Science and Technology, Univ. Nebraska, Lincoln, Nebr. 68503); Bullerman, L. B. *J. Milk Food Technol.* 38(11):695-705; 1975.

Patulin (4-hydroxy-4H-furo[3,2c]pyran-2(6H)-one) is a metabolite of numerous *Aspergillus* and *Penicillium* species. It is toxic to some microorganisms, plants and animals, and carcinogenic to mice. It appears that man would be susceptible to the toxic effects of this compound. The possibility that patulin production could occur during refrigerated storage is real. However, the reactivity of patulin with sulfhydryl groups and other food components may cause its apparent disappearance from a food product. Apparently toxicity is lessened. Low pH or reaction with digestive enzymes might reverse these reactions or liberate free patulin in the gut. Certain foods such as cheeses and cured meats do not appear to support patulin production to any great extent. This, combined with the reactivity of patulin with sulfhydryl groups, seems to lessen the danger of patulin occurrence in these foods. However, apple products and grain products may pose more of a potential problem. Apple products are of particular concern since common apple rotting molds are frequent producers of patulin. Natural contamination with patulin has been found only in apple sap, juice, and cider (49-309 ppb). (143 references)

2402 BINDING OF AROMATIC AMINES TO DNA AND RNA. (Eng.) Kriek, E. (Netherlands Cancer Inst., 108 Sarphatistraat, Amsterdam, Netherlands). *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 36-40.

The reaction products of covalently bound derivatives of aromatic amines with RNA and DNA *in vivo* are discussed. *N*-hydroxy-aminofluorene (-AF) reacts nonenzymatically in acid-catalyzed reactions with glutamine in RNA and DNA. The synthetic ester of *N*-acetoxy-2-acetylaminofluorene (-AAF) reacts with guanosine, deoxyguanosine, RNA, and DNA. A similar interaction has been demonstrated *in vivo* following enzymatic degradation of RNA and DNA from the livers of male rats treated with AAF-9-^{14}C or N-hydroxy-AAF-9-^{14}C, yielding *N*-(guanosin-8-yl)-2-AAF as the major reaction product in RNA. In DNA, over 70% of the entity attached to guanine was AF. The actual reactive form responsible for the binding of AAF and AF to DNA is unknown, but may involve *N*-hydroxy-AAF esters in the *in vivo* binding to DNA. A second component that is present only in DNA and responsible for the persistent binding of -AAF is 3-(guanine-N^2-yl)-2-AAF; a similar product has been isolated *in vitro* from DNA reacted with *N*-acetoxy-AAF or *N*-OSO_3K-AAF. The extent of the reaction of adenine with DNA or RNA is low, and does not exceed 3-4% of the total substitution. The sulfate of *N*-hydroxy-N-4-acetylaminobiphenyl reacts in a similar manner as guanosine to *N*-acetoxy-AAF to yield *N*-(guanosine-8-yl)-4-acetylaminobiphenyl. This compound and the corresponding deacetylated derivative have been detected in rat RNA treated with *N*-hydroxy-acetylaminobiphenyl esters of other carcinogenic arylhydroxamic acids reacted similarly with guanosine. Esters of *N*-hydroxy-2-acetylaminophenanthrene react equally well with adenosine and guanosine. In model experiments with *N*-acetoxy-AAF and nucleic acids *in vitro,* no *N*-acetyl groups have been lost in aqueous solutions. Once the *N*-acetyl group is removed, the resulting *N*-(guanine-8-yl)-2-AF moiety becomes unstable. This reaction may represent a mechanism by which release of the bound carcinogen leads to an altered nucleic acid. In addition, the role of guanine in nucleic acid structure is discussed. The authors suggest the possibility that the proton released by substitution of the 8-carbon of guanine would account for the reactivity of DNA to *N*-acetoxy-AAF and other arylhydroxamic acid esters. (21 references)

2403 FUNCTION AND HOMEOSTASIS OF COPPER AND ZINC IN MAMMALS. (Eng.) Fisher, G. L. (Radiobiology Lab., Univ. California, Davis, Calif. 95616). *Sci. Total Environ.* 4(4):373-412; 1975.

The biochemical and physiological functions of the micronutrients copper and zinc are reviewed; special attention is given to the maintenance of homeostatic levels, the physiologic changes associated with deficiency states, and the physiochemical properties of copper and zinc biomolecules. Trace elements are defined, and the general roles of essential, and non-essential trace elements are discussed. Hazardous trace elements are also noted. The characteristics and properties of metalloenzymes and metal ion activated enzymes are summarized, and direct and indirect interactions with enzyme systems are noted. A discussion of copper as a micronutrient notes the source and functions of the major copper metalloenzymes, and tabulates the levels of copper in tissues and fluids of numerous species; serum copper levels as a function of age in humans are graphically represented. Numerous effects of primary and secondary copper deficiencies are described in detail. Studies of the isolation, characterization, distribution, and function of the serum copper enzyme ceruloplasmin are also detailed, and a scheme for ceruloplasmin-iron interaction is proposed. Disease and environmental factors affecting serum copper levels in humans are summarized. In addition to the circadian pattern noted, serum copper levels are also found to reflect the activity of efficiency of treatment of leukemia, malignant lymphoma, osteosarcoma, and mammary cancers. Attempts to evaluate the physiologic and biochemical function of zinc also note its nonuniform distribution in biologic tissues and fluid of various species. The role of zinc in metalloenzymes, as enzyme activators, and associated with polypeptides, nucleotides, and other macromolecules is also acknowledged. The major zinc metalloenzymes of carbonic anhydrase, carboxypeptidase, alkaline phosphatase, and liver alcohol dehydrogenase are especially noted. The characteristics of zinc deficiency in higher animals are described, and the associated biochemical changes are discussed. In addi-

tion to noting the *in vitro* requirements of zinc, the zinc requirements of neoplastic growth are discussed. Changes in serum and plasma zinc levels in human tissues and fluid are reported, and the effects of radiation on zinc levels, uptake, and metabolism are described. However, the exact mechanisms of many of the effects noted are not yet determined. (176 references)

2404 THE CARCINOGENICITY OF DIELDRIN. PART II. (Eng.) Epstein, S. S. (Medical Sch., Case Western Reserve Univ., Cleveland, Ohio). *Sci. Total Environ.* 4(3):205-217; 1975.

Further results of investigations on the carcinogenicity of Dieldrin are reported. A standard definition of chemical carcinogens, i.e. agents that increase the probability of induction of benign or malignant tumors, is presented. Attempts are made to discount the significance of the Dieldrin-induced carcinogenicity data in mice, due to a high variability in their spontaneous hepatic tumors. However, numerous independent studies reveal an enhanced frequency of "type a" tumors after Dieldrin treatment; an increase from 0-47% of "type b" tumors in female mice has also been found. Despite claims that human babies are at no greater, or even at a lesser risk to Dieldrin carcinogenesis than the general population, newborn animals have been repeatedly shown more sensitive to carcinogenic effects than adult animals. Enhanced sensitivity to aflatoxin B_1, 3-methylcholanthrene, urethane, dimethylnitrosamine, condensed cigarette smoke, and organic extracts of particulate atmospheric pollutants has been demonstrated in infant animals. Much experimental data has indicated that the enhanced sensitivity to carcinogenicity relates to lipid-soluble carcinogens, such as Dieldrin. The carcinogenic effects of Dieldrin are both dose-dependent and time-dependent. In the assessment of policies regarding the regulation of Dieldrin use, the carcinogenicity demonstrated in several strains of mice, the close parallelism of cancers seen in humans and animals, and the involuntary nature of human exposure sbuld all be taken into account. Although no "safe" levels of carcinogens can be determined, continued Dieldrin exposure is an imminent hazard. (19 references)

2405 ORAL CONTRACEPTIVES: RELATION TO MAMMARY CANCER, BENIGN BREAST LESIONS, AND CERVICAL CANCER. (Eng.) Drill, V. A. (Coll. Medicine, Univ. Illinois, Medical Center, Chicago, Ill. 60680). *Annu. Rev. Pharmacol.* 15:367-385; 1975.

The relationship of oral contraceptives to mammary cancer, benign breast lesions, and cervical cancer is reviewed. The type of response obtained depends largely on the species and strain of animal that is employed. A variety of clinical studies has failed to demonstrate that estrogen can cause mammary cancer. Similar relationships exist for oral contraceptives, and the clinical data show good agreement in demonstrating that the contraceptive steroids do not have a tumorigenic effect on the human mammary gland. Estrogen can increase the occurrence of cervical cancer in certain strains of mice, but apparently this effect is not observed in other species of animals, including man. The preponderance of data to date shows that oral contraceptives do not adversely affect the occurrence of abnormal Papanicolaou smears, cervical dysplasia, cervical cancer *in situ*, or invasive cervical cancer. (149 references)

2406 ORAL CONTRACEPTIVE HORMONES, FOLATE METABOLISM, AND THE CERVICAL EPITHELIUM. (Eng.) Lindenbaum, J. (Harlem Hosp. Cent., New York, N.Y.); Whitehead, N.; Reyner, F. *Am. J. Clin. Nutr.* 28(4): 346-353; 1975.

Evidence concerning disturbances in folate metabolism in women using oral contraceptive agents is reviewed, and controversial and contradictory findings are noted. The etiologic relation of oral contraceptives to megaloblastic anemia is questioned, and an alternative proposal is raised that contraceptive steroids may have only a slight or subtle effect on folate status; they may act as a contributory or precipitating factor in patients with other underlying disorders. Controversy exists as to the effect of oral contraceptive therapy on serum folate concentrations, RBC folate concentrations, and serum vitamin B_{12} concentrations. Decreased pteroylpolyglutamate absorption has been reported. Additional reports suggest selective polyglutamate folate malabsorption and variable inhibition of folate conjugase. Reversible morphologic abnormalities in the cervical epithelium have been well documented in patients with systemic vitamin B_{12} and folic acid deficiencies. Although megaloblastic Papanicolaou-stained cervicovaginal smears were reported in 19% of 115 women on oral contraceptives in one study, no association could be subsequently claimed between the presence of an abnormal smear and systemic folate deficiency. Follow-up studies revealed a recurrence of the characteristic megaloblastic abnormality in women previously treated with folic acid and continuing use of oral contraceptives; no evidence of premalignant changes was observed. While the relation to premalignant changes remain a controversy, the nuclear changes in a series of patients with megaloblastic cervical smears differ from those found in patients with dyskaryosis of dysplasia. A discussion of possible mechanisms is included. It is proposed that contraceptive hormone therapy frequently leads to a local depletion of folate coenzymes, resulting in abnormalities of DNA synthesis by cervicovaginal cells. However, the effect on folate utilization would contribute to the development of systemic folic deficiency severe enough to cause a megaloblastic anemia only in the rare patient with some other underlying disorder of folate supply, absorption or metabolism. (73 references)

2407 TRACE ANESTHETIC EXPOSURE: CONSEQUENCES AND CONTROL. (Eng.) Neufeld, G. R. (Dept. Anesthesia, Univ. Pennsylvania, 3400 Spruce Street, Philadelphia, Pa.); Lecky, J. H. *Surg. Clin. North Am.* 55(4):967-973; 1975.

Evidence that chronic exposure to trace levels of anesthetic gases is hazardous is presented, and the

means available for measurement and control of trace anesthetic levels are discussed. Epidemiologic and animal studies indicate that chronic exposure to anesthetic gases may constitute a potential health hazard. This is suggested by a higher incidence of spontaneous abortion among female operating room personnel, congenital anomalies in the offspring of operating room personnel, and neoplasia of the reticuloendothelial system. Human data show that performance can be compromised during exposure to anesthetic traces. A direct cause and effect relationship between anesthetic exposure and the alleged hazards will require further prospective studies. In the interim, monitoring programs should be established to define adequate clearances of the anesthetic agents. Minimum standards and recommended procedures should be established regarding operating room ventilation and design. The use of effective scavengers and anesthetic techniques not requiring the use of inhalational agents should be encouraged. (17 references)

2408 INHALATION ANESTHETICS--MORE VINYL CHLORIDE? (Eng.) Corbett, T. H. (No affiliation given). *Environ. Res.* 9(3):211-214; 1975.

Studies on the hazards of anesthetic gases to operating room personnel are reviewed. The review includes a nation-wide survey of 50,000 operating room professionals and of 24,000 unexposed medical professionals (controls). In this study, the incidence of spontaneous abortion in exposed female personnel was 1.3-2 times the incidence in unexposed controls. Woman physicians had the highest risk, followed by nurse-anesthetists. The incidence of congenital abnormalities among live-born offspring of female physician-anesthetists was double that among offspring of unexposed female physicians. Among nurse-anesthetists, the risk of fetal abnormalities was 1.6 times that of their unexposed counterparts. The frequency of cancer was 1.3-2 times greater among exposed women; again, the highest risk was among women physician-anesthetists, followed by nurse anesthetists. Liver disease, excluding serum hepatitis, was 1.3-2.2 times more common among woman anesthetists than among their unexposed counterparts. A similar increase in liver disease was seen in male physician-anesthetists compared with male pediatricians. A comparison of the chemical structures of isoflurane, methoxyflurane, enflurane, and trichloroethylene with that of known human carcinogens indicates that these anesthetic agents must be considered as possible carcinogens. The chemical structure of trichloroethylene is similar to that of vinyl chloride. The installation of gas scavenging devices is recommended to reduce the risk to operating room personnel of anesthetics that may be embryolethal, teratogenic, mutagenic, or carcinogenic. (10 references)

2409 PLUTONIUM IN MAMMALS: INFLUENCE OF PLUTONIUM CHEMISTRY, ROUTE OF ADMINISTRATION, AND PHYSIOLOGICAL STATUS OF THE ANIMAL ON INITIAL DISTRIBUTION AND LONG-TERM METABOLISM. (Eng.) Durbin, P. W. (Lawrence Berkeley Lab., Univ. California, Berkeley, Calif. 94720). *Health Phys.* 29(4):495-510; 1975.

Current concepts of plutonium (Pu) metabolism are reviewed. Both the amounts and rates of Pu absorption from the gastrointestinal tract, wound sites, or the lung decrease in the order: soluble complexes > hydrolyzable salts > insoluble compounds. Absorption of Pu from the gastrointestinal tract is greater in very young animals than in adults. Deposition of Pu in bone is greater in growing animals than in young adults. When introduced as a metabolizable complex or simple salt, Pu is transported in plasma chiefly by transferrin. Circulating as the Pu-transferrin complex, Pu is deposited as single atoms in liver parenchymal cells and at the cell-mineral interface of those bone surfaces in closest proximity to erythropoietic marrow. Liver deposition is favored when Pu is introduced directly into the body by parenteral injection. Skeletal deposition is favored when Pu has been transported across cell barriers as in the case of ingestion or inhalation. In the dog, Pu in hepatic cells is initially associated with soluble ferritin, and later with subcellular structures. Upon the death of hepatic cells, Pu-laden debris accumulates in liver reticuloendotheial (RE) cells. Some of the phagocytized Pu is eventually released from the liver. Concentrations of Pu on bone surfaces decrease in the order: endosteal > periosteal > Haversian. Plutonium concentrations on endosteal surfaces decrease in the order: resorbing > resting > growing. Bone surfaces labeled with Pu may remain unchanged, be buried by formation of new bone, or be reabsorbed by osteoclasts. Some resorbed Pu is dissolved and recirculated, and may be redeposited in the skeleton. Apparently some of the Pu in resorbed bone cannot be dissolved and accumulates in osteoclasts in the marrow. Following death of the osteoclasts, the Pu is taken up by marrow RE cells, which slowly disappear from the marrow. Insoluble Pu compounds initially deposited in lung or beneath the skin may gradually enter the body without having been dissolved, and pass by way of RE cells into the lymph and local lymph nodes, and ultimately into RE cells in liver, spleen, and bone marrow. (2 references)

2410 SKELETAL AND TISSUE LESIONS RESULTING FROM EXPOSURE TO RADIUM AND FISSION PRODUCTS. (Eng.) Warren, S. (N. Engl. Deaconess Hosp., Boston, Mass.). *Ann. Clin. Lab. Sci.* 5(2):75-81; 1975.

The effects of absorbed radionuclides and external radiation on bone and tissue are reviewed. The physical-chemical nature of the bone-seeking radioactive isotopes largely determines their ultimate effects. Those in soluble form are initially widely diffused in the body; they are then partially excreted and partially concentrated. Those in particulate form experience localization according to their means of access into the body, then redistribution by phagocytosis or slow solution; liver and lungs may be exposed in addition to bone. ^{226}Ra tends to be deposited locally more in cortical bone than trabecular and may be localized in several adjacent Haversian systems. It is about equal in patchy distribution near periosteum and endosteum. Thorium deposits mainly in the endosteum of both trabecular and cortical bone. It involves some Haversian systems, as does plutonium. Americum, less effec-

tive in inducing bone tumors than plutonium, is widely and equally distributed in endosteal and periosteal bone. The chief effects of absorbed radionuclides and external radiation are radiation osteitis, characterized by pain and evidence of rarefaction of bone; disturbed bone growth; spontaneous fractures; myelofibrosis; and bone tumors, including osteogenic sarcoma near the epiphyses, fibrosarcomas, and plasma cell myeloma. Another result of radium poisoning is cancer of the mucous membrane of the sinuses. In a survey of radiation-induced osteogenic sarcomas, a practical threshold is observed of 1,111 rads, implying a permissible burden of 0.1 mCi of ^{226}Ra. (14 references)

2411 SUNLIGHT, SKIN CANCER, AND SUNSCREENS. (Eng.) Kaminester, L. H. (Suite 201B, The Gentry, 860 US Highway 1, North Palm Beach, Fla. 33408). *J.A.M.A.* 232(13):1373-1374; 1975.

Effects of acute or prolonged exposure to UV light and measures to prevent or minimize such effects are discussed. On acute exposure, the erythrogenic spectrum causes not only sunburn but may also induce phototoxic and photoallergic reactions and precipitate changes such as xeroderma pigmentosum, solar urticaria, and systemic lupus erythematosus. A single exposure to erythrogenic UV light has been shown to inhibit DNA, RNA, and protein synthesis in human skin. Prolonged exposure to UV light may lead to the development of premalignant and malignant skin lesions, primarily actinic keratosis, basal cell carcinomas, and squamous cell carcinomas. The actinic or solar keratosis is found predominantly in sunny climates, on white-skinned persons who often have a poor ability to tan and may progress to frank squamous cell carcinoma. The basal cell carcinoma is usually a round or oval lesion with central depression, superficial telangiectasis and a gray or translucent pearly border. Some lesions also contain melanin. The squamous cell carcinoma has a variable clinical picture, from a small, firm, red nodule to a red, verrucose or scaly growth. Squamous cell carcinomas arising in sun-damaged areas have a far lower incidence of metastasis than do squamous cell carcinomas arising in scars or *de novo*. The most important factor in prevention of these unpleasant skin disorders is to avoid excessive sun exposure. There are two types of sunscreens, physical and chemical blockers. The physical blockers deflect and scatter light, providing a barrier to sunlight penetration. They have the general advantage of giving more inclusive coverage over a wider range of the UV spectrum, but are not cosmetically acceptable. The chemical sunscreens absorb light of a particular wavelength. While they are usually more cosmetically acceptible, they have several disadvantages, including sensitization or primary irritation and nonuniform coverage of the complete UV spectrum. The absorption characteristics and clinical efficacy studies performed with aminobenzoic acid indicate that it is one of the best agents for protection within the erythrogenic spectrum. Systemic photoprotective agents have not found widespread acceptance. Drugs such as indomethacin and aspirin, which cause a dramatic decrease in the erythema and elevated skin temperature of sunburn, may actually be deleterious in the long run by masking the acute changes of sun exposure while doing nothing to prevent the long-term sequelae. (12 references)

2412 NEWER KNOWLEDGE IN COMPARATIVE VIROLOGY--ITS CONTRIBUTION TO HUMAN HEALTH RESEARCH. (Eng.) Cabasso, V. J. (Cutter Labs. Inc., Berkeley, California). *Vet. Rec.* 96(26):563-566; 1975.

Progress in the field of comparative virology is reviewed. The study of Marek's disease found application in that of Burkitt's lymphoma, and may lead to a possible vaccine against the human disease. Equally useful information came from the study of canine distemper in the development of a chorio-allantoic membrane attenuated measles vaccine, and in present knowledge of subacute sclerosing panencephalitis (SSPE) of humans; from the study of reovirus-like agents of infant mice and neonatal calves in that of an acute nonbacterial gastroenteritis of infants and young children; and from that of the cancer-producing viruses of chickens, cats, and dogs to a better understanding of some human neoplasias. Finally, Aleutian mink disease may be an excellent natural model for the study of the collagen diseases of man, and scrapie of sheep one for that of a human chronic degenerative disease of the central nervous system of humans such as Kuru. It is concluded that the comparative study of viruses has allowed more rapid progress in the knowledge and control of human pathogenic viruses, and that this approach to the study of viral diseases should be continued. (46 references)

2413 EPSTEIN-BARR-VIRUS-(EBV)-ANTIGENS. (Eng.) Diehl, V. (Hämatologisch-onkologische Abteilung, Medizinische Hochschule Hannover, West Germany). *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 182-187.

Epstein-Barr virus (EBV) macromolecules can be detected by immunological and biochemical means *in vitro* and *in vivo*. There exist at least four different EBV-associated antigens. The EBV-nuclear antigen (EBNA) may reflect a T antigen. Its appearance correlates in 100% to the presence of the EBV DNA. *In vivo*, restriction of the virus genome permits only the expression of EBNA and membrane antigen. The mechanisms of this restriction are still unknown. Virus particles have not yet been detected in biopsy material by electron microscopy. EBV-specific macromolecules have been discovered *in vivo* in two different cell types, the lymphoblastoid cells (B-cells) and the epithelial cells in nasopharyngeal carcinoma. Both cell types represent transformed cells. Thus far, the permissive *in vivo* cell for EBV has not been detected. *In vitro*, EBV is found exclusively in B-lymphocytes. T-cells do exclude infection by EBV and show no production of EBV associated products. Three types of B-lymphoblastoid cell lines exist with regard to EBV-macromolecule synthesis: (a) EBV-negative

lines without production of EBV DNA, EBV antigens, or virus particles, (b) EBV nonproducing lymphoblastoid lines with the presence of the EBV genome and the expression of the EBNA, but no virus particle synthesis, and (c) EBV-producing lines with the expression of early and late EBV proteins and production of virus particles. Infection of primary fetal lymphocytes with the P_3-HR-1-EBV leads to cell death; no viral products have been demonstrated thus far within these cells. Infection with the transforming variant (B_{95}-8-EBV) EBV leads to transformation of lymphocytes with the expression of all or part of the viral macromolecules. (30 references)

2414 AVIAN RNA TUMOR VIRUSES: A MODEL FOR STUDYING TUMOR ASSOCIATED CELL SURFACE ALTERATIONS. (Eng.) Kurth, R. (Imp. Cancer Res. Fund Lab., London, England); Bauer, H. *Biochim. Biophysc. Acta* 417(1):1-23; 1975.

A description of the avian tumor virus system, the biochemical detection of membrane changes in avian tumor virus-transformed cells, and immunological detection of membrane changes in those transformed cells is presented. Avian RNA-containing tumor viruses are C-type viruses, and are classified into avian sarcoma and avian leukosis viruses. The biological properties of individual strains are distinct with respect to the histological type of target cell. Studies attempting to establish consistent differences in the biochemical composition of malignant and corresponding normal cells measure the relative content and distribution of sialic acid, glycolipid, phospholipids, glycoproteins, plus the differential interaction of cell surfaces with lectin. *In vivo* studies of tumor-specific transplantation antigens suggest a group-specificity for various avian sarcoma virus strains; contrasting experiments indicate transplantation immunity induced only by virus envelope antigen. *In vitro* studies of tumor antigens demonstrate the existence of two kinds of virus-directed cell surface antigens: the virus envelope antigens and the tumor-specific cell surface antigen system. Evidence is presented for the existence of common tumor antigens on avian tumor virus-transformed cells of different species, common tumor antigen on avian tumor virus-transformed sarcoma and leukemia cells, and for the re-expression of embryonic antigen paralleling transformation by avian sarcoma virus. The use of virus mutants in cell membrane studies indicates that continuous expression of certain viral genome products is linked with the transformed phenotype of the mutant-infected cells, and that synthesis of the gene product is inhibited under nonpermissive conditions. In investigating the immunological significance of new cell surface antigens, the demonstration of humoral and cellular immunity against tumor cells in the avian tumor virus system agrees with the general concept of 'immune surveillance'. Four possibilities are presented for the origin of tumor-specific cell surface antigen, plus the suggestion that it may represent a complex of several antigens, including species-specific and interspecies-specific antigens. (135 references)

2415 NEUROBLASTOMA, IMMUNODEFICIENCY, AND CATECHOLAMINES. (Eng.) Wood, L. (1188 North Euclid, Anaheim, Calif. 92801). *Lancet* 1 (7915):1091-1092; 1975.

The potential of the immune system in the prevention and the response to treatment of malignancy is discussed. It is acknowledged that patients with congenital immunodeficiency have an increased incidence of neoplasia, that many human neoplasms have tumor-specific antigens, and that cancer patients with immunological deficiency have a poor prognosis; the importance of immunocompetence in cancer patients is suggested. Adrenaline is noted to modify a wide variety of immune processes by increasing leukocyte cyclic-AMP levels, thus inducing production or secretion of antibody. Patients with neuroblastoma are in double jeopardy--from a malignant tumor and from the substances it may elaborate which specifically impair their immune responses. Although urinary adrenaline is generally found within the normal range, various catecholamine precursors and metabolites are increased in neuroblastoma patients. Whereas adrenaline may be of trivial importance, the possibility of such compounds of similar structure stimulating B-adrenergic receptors prompts the suggestion that adjuvant treatment with B-adrenergic antagonists may improve the prognosis in patients with neuroblastoma. (6 references)

2416 CURRENT STATUS OF CARCINOEMBRYONIC ANTIGEN ASSAY. (Eng.) Chu, T. M. (Roswell Park Memorial Inst. and State Univ. New York at Buffalo, Buffalo, N.Y.). *Semin. Nucl. Med.* 5(3):255-262; 1975.

The usefulness of carcinoembryonic antigen (CEA) in the detection and diagnosis of cancer was evaluated. CEA is a glycoprotein that can be measured by radioimmunoassay and other immunologic techniques. The CEA reagent is currently commercially available in kit form and has been found to be satisfactory for laboratory use. The highest percentage of elevated plasma CEA and the highest CEA titer have been found in patients with entodermally derived tumors. Current CEA reagents do not assist in the differential diagnosis of tumors, however. CEA has also been detected in patients with other tumors and in patients with nonneoplastic disease, as well as in heavy cigarette smokers. The present CEA assay cannot be used to screen for cancer in the general population. The greatest clinical usefulness of current CEA assay is in assessing prognosis, in the detection of residual tumors and recurrent disease, and in monitoring chemotherapy and radiotherapy. The use of radioactive anti-CEA antiserum as a tumor-localizing agent may be of potential value in the future. (35 references)

2417 MITOGENS AND T-CELL HETEROGENEITY. (Eng.) Dutton, R. W. (Dep. Biol., Univ. California, San Diego). *Ann. N.Y. Acad. Sci.* 249:43-46; 1975.

The results of a study on the effect of concanavalin A (Con A) on the *in vitro* immune response of normal mouse spleen cell suspensions are reviewed. Con A added to spleen cell suspensions stimulated thy-

midine incorporation and inhibited primary and secondary IgM response to SRBC or burro RBC (BRBC) or the anti-trinitrophenyl (TNP) response to TNP-SRBC. Optimal response occurred at 2 μg/ml Con A. No inhibition was observed when Con A was added 24 hr after the culture initiation. The inhibitory effects of Con A were also abolished by treatment with goat anti-mouse brain antisera followed by complement or by X-irradiation. In the absence of inhibitory effects, Con A induced a stimulatory effect on the immune response of heterologous RBC. The cell-mediating stimulatory effect was present after treatment with goat anti-mouse brain and complement, in AT x BM mice, and persisted in adult thymectomized mouse spleens long after thymectomy. It was present in lymph node cells, but not in thymus, and was also not found in the spleens of nu/nu mice. Spleen cell suspensions preincubated with Con A for 24 hr inhibited the humoral response of fresh syngeneic spleen cells in the absence of Con A. The author stresses the need to remember that the data reported here represent net effects, which result from combined inhibitory and stimulatory effects. He concludes that because activity was absent from nu/nu mouse spleens, both the inhibitory and stimulatory activities are mediated by T cells and proposes that the Con A-induced activities are mediated by two separate T cell types. (6 references)

2418 IMMUNITY AND TUMORS OF THE NERVOUS SYSTEM. (Eng.) Brooks, W. H. (VA Hosp., Lexington, Ky., 40506); Netsky, M. G.; Levine, J. E. *Surg. Neurol.* 3(4):184-186; 1975.

The immunological privileged site of the brain, with respect to the lack of immune response to antigens within the brain, appears only relative. Animals bearing a methylcholanthrene-induced ependymoma transplant, either intracranial or sc, and subsequently cured by irradiation, show a 37% rejection of a second cerebral implant in the first group and 64% in the second; this indicates that somewhat greater immunity was induced by sc implants than by implants within the brain. Patients with primary tumors of the CNS show a cell-mediated response against their own tumor cells in culture. Blocking antibodies against glial tumor cells are demonstrable, but are lost postoperatively. Sera of 17 of 26 patients with astrocytomas have been shown to be cytotoxic to tumor cells grown in culture. Prior immunization of mice with brain tumor cells brings about significant inhibition and rejection of challenge inoculations of the tumor. A scientific approach to immunotherapy against tumors of the nervous system in man requires precise antigenicity of the tumor tissues, because surrounding normal brain may have related antigens and may be subject to destruction by autoimmune mechanisms. The immunotherapeutic approach thus appears highly speculative. This approach may be highly dangerous because of the nonspecificity of anti-glioma antibodies, the evidence of shared antigens between brain and lymphoid tissue, and the danger of the production of enhancing antibodies augmenting tumor growth. (36 references).

2419 THE EPIDEMIOLOGY OF NON-HODGKIN'S LYMPHOMAS. (Eng.) Wright, D. H. (Southampton General Hosp., Southampton S09 4XY, England). *Proc. Int. Cancer Congr. 11th.* Vol. 6 *(Tumors of Specific Sites).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 356-362.

Many problems affect the epidemiological study of nonHodgkin's lymphomas. These problems will not be solved until a satisfactory, biologically significant, classification that can be universally applied is devised and then incorporated into the International Classification of Disease Index. In the meantime, a number of interesting epidemiological situations have emerged as a result of reports from single institutions and national registries. Three of these, Burkitt's lymphoma, the Middle East abdominal lymphoma, and the association of tumors of the lymphoreticular system with immunodeficiency states, are discussed. Etiological factors that may be involved in all three situations include oncogenic viruses, immunosuppression, and immunostimulation with the breakdown of self-regulatory control mechanisms. (30 references)

2420 BREAST CANCER, ETIOLOGIC FACTORS IN MAN. (Eng.) de Waard, F. (Inst. Social Medicine Univ. Utrecht, Netherlands). *Proc. Int. Cancer Congr. 11th.* Vol. 6 *(Tumors of Specific Sites).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 14-17.

Recent developments concerning the etiologic nature of human breast cancer are presented. Although virologists continue to study the relation between lactation and human breast cancer, epidemiologists have undermined this theory by collecting information on cancer incidence throughout the world. Comparisons between countries suggest the risk experienced by populations in prosperous western countries as an important etiologic factor. Age at first parity accounts for only a small proportion of the differences between incidence rates of Japan and the U. S. However, incidence figures for the American Japanese are rising to Western levels. Body height and weight are risk factors mainly in postmenopausal women; in the Netherlands, tall and heavy women had five-fold the risk of short and slender women. Body weight is largely dependent on current energy supply, while body height reflects genetic and environmental stimuli. Therefore, the causal factor for the rise in breast cancer incidence among the American Japanese seems to be due to a quicker effect of weight and a slower effect of height. In addition, the role of estrogens and androgens and their relative importance to breast cancer is discussed. Estrogen receptors are found in about 50% of primary cancers and it has been demonstrated that androstenediol (physiological dose) is capable of blocking estrogen receptor sites. The author suggests that over the next four yr, human breast cancer studies should include the role of nutritional factors, and the application of immunology and host resistance studies

or the early diagnosis of breast cancer. (No eferences)

2421 ESTROGEN RECEPTOR ASSAY IN HUMAN BREAST CANCER. (Eng.) Korenman, S. G. (San Fernando Valley Medical Program, Univ. California at Los Angeles, Calif. 91343). *J. Natl. Cancer Inst.* 55(3): 543-545; 1975.

The various methods of steroid receptor assay in breast cancer discussed at a Workshop on Receptor Assay in Breast Cancer Tissue at the Fourth International Congress on Hormonal Steroids held in Mexico City, September 2-7, 1974 are reviewed. Data are also presented on the percentage of estrogen receptor-positive primary and metastatic breast cancers reported by various investigators; on the relation of estrogen receptor content to response to endocrine management; and on the variety of therapies attempted in receptor-positive and receptor-negative patients with advanced breast cancer. In one study, tumors lacking estrogen receptor rarely responded to an endocrine-directed therapy; those that were positive had a 57% response rate. An important factor in response failure is related to the role of estrogen in promoting duct elongation and facilitating prolactin release from the pituitary gland. To the extent that prolactin stimulates tumor growth and estrogen withdrawal fails to reduce prolactin secretin, there will be treatment failure. Some therapeutic failures may be related to the subcellular mechanisms of steroid hormone action. The value of estrogen receptor assay is in the identification of patients for whom endocrine management would be fruitless. Endocrine management will continue to be used as long as it effectively enhances the results from other therapies. However, the primary function of endocrine management in metastatic breast cancer will decline with the development of more efficient cytotoxic chemotherapy, adjuvant chemotherapy, and immunotherapy. (16 references)

2422 THE RECENT EXCITEMENT IN THE DNA GROWING POINT PROBLEM. (Eng.) Dressler, D. (Dept. Biochemistry and Molecular Biology, Harvard Univ., Cambridge, Mass. 02138). *Annu. Rev. Microbiol.* 29: 525-559; 1975.

Molecular mechanisms involved in DNA replication, especially as studied in microorganisms, are reviewed. Data are integrated from two experimental approaches, regarding both the molecular architecture and the enzymatic events at the DNA growing point. A discussion of overall models of DNA replication cites viral T7 DNA replication, the *Drosophila* DNA replication mechanism, the Cairns pattern, and the rolling circle pattern. Key points demonstrated by all the replication patterns discussed are the existence of an origin of DNA synthesis, and the procession *via* growing points. Investigations into the biochemistry of the DNA growing point note the roles of classic DNA polymerase I, DNA polymerase II and III, and the 5'-3' exonuclease activity of DNA polymerase I. While all DNA polymerases appear to employ the same basic reaction mechanism, none can function as isolated proteins. Further investigations into the DNA growing point problem suggest two alternative solutions: existence of a 5'-3' DNA polymerase, or net elongation *via* discontinuous synthesis. Results support an optional discontinuous synthesis of both daughter strands. A knife and fork model proposed for the formation of the DNA fragment falters due to the disagreement with experimental predictions. However, using the single-stranded DNA phages ϕX and M13 as an experimental system, a rolling circle intermediate capable of forming both double-stranded and single-stranded progeny DNA is supported. Studies on initiating DNA strands *de novo* note the use of preformed oligonucleotides and of RNA oligonucleotides synthesized *in situ* as primers. The uniform size of the RNA moiety, the presence of initiating triphosphate end groups, and the copurification of the RNA with DNA fragments support the RNA primer hypothesis. A postulated replisome is discussed, and a teleological concept that initiating a DNA fragment with RNA facilitates the recognition, excision, and repair of any probable mistakes is presented. (223 references).

2423 A CRITICAL REASSESSMENT OF THE EVIDENCE BEARING ON SMOKING AS THE CAUSE OF LUNG CANCER. (Eng.) Sterling, T. D. (Dep. Appl. Math. Comput. Sci., Washington Univ., St. Louis, Mo.). *Am. J. Public Health* 65(9):939-953; 1975. (116 references)

2424 SACCHARIN AND BLADDER CANCER. (Eng.) Anonymous. *Br. Med. J.* 3(5984):610;1975. (6 references)

2425 ENCYCLOPEDIA OF FOOD CHEMICALS. (Eng.) Anonymous. *Food Can.* 35(4):33-56; 1975. (1 reference)

2426 CARCINOGENIC AGENT? (Eng.) Anonymous. *Nature* 257(5529):735; 1975. (No references)

2427 BACKGROUND INFORMATION ON TRICHLOROETHYLENE. (Eng.) Lloyd, J. W. (Office Occupational Health Surveillance and Biometrics, NIOSH, 5600 Fishers Lane, Rockville, Md. 20852); Moore, R. M., Jr.; Breslin, P. *J. Occup. Med.* 17(9):603-605; 1975. (20 references)

2428 BENZPYRENE--CARCINOGENIC RISKS. (Swe.) Sandberg, C. G. (Hagfors Jarnverk, S-683 01 Hagfors 1, Sweden). *Lakartidningen* 72(33):3081-3083; 1975. (32 references)

2429 METABOLIC ACTIVATION AND REACTIVITY OF CHAMICAL CARCINOGENS. (Eng.) Miller, J. A. (Univ. Wisconsin Medical Center, Madison, Wis. 53706); Miller, E. C. *Mutat. Res.* 33(1):25-26; 1975. (4 references)

2430 CARCINOGENS ARE MUTAGENS: A SIMPLE TEST SYSTEM. (Eng.) Ames, B. N. (Dept. Bio-

chemistry, Univ. California, Berkeley, Calif. 94720); McCann, J.; Yamasaki, E. *Mutat. Res.* 33(1):27-28; 1975. (9 references)

2431 CANCER AT WORK. (Eng.) Anonymous. *Nature* 257(5523):170-171; 1975. (No references)

2432 VINYL CHLORIDE--AN EXAMPLE OF NEGLECTED RISK IN THE WORKING ENVIRONMENT. (Swe.) Olin, R. (Health Center, Technical Univ., Stockholm, Sweden). *Lakartidningen* 72(7):540-541; 1975. (26 references)

2433 PRELIMINARY ASSESSMENT OF THE ENVIRONMENTAL PROBLEMS ASSOCIATED WITH VINYL CHLORIDE AND POLYVINYL CHLORIDE. (Eng.) Anonymous (Environmental Protection Agency, Washington, D.C. Office of Toxic Substances). 106 pp., 1974. [available through National Technical Information Services, Washington, D.C. Document No. PB-239 110/OWP].

2434 CHARACTERIZATION AND CONTROL OF ASBESTOS EMISSIONS FROM OPEN SOURCES. (Eng.) Harwood, C. F. (IIT Res. Inst., Chicago, Ill.); Blaszak, T. P. 204 pp., 1974. [available through National Technical Information Services, Washington D.C. Document No. PB-238 925/2GA].

2435 BIOLOGY OF AVIAN RNA RUMOUR VIRUSES. (Eng.) Hlozanek, I. (Inst. Experimental Biology and Genetics, Czechoslovak Acad. of Sciences, Prague, Czechoslovakia). In: *Reviews in Leukaemia and Lymphoma, 1--Advances in Acute Leukaemia* edited by Cleton, F. J.; Crowther, D.; Malpas, J. S. Amsterdam, North Holland Publishing Co., 1974, pp. 229-301. (460 references)

2436 C-TYPE VIRUSES IN CHIMPANZEE (*PAN* SP.) PLACENTAS. (Eng.) Kalter, S. S. (Southwest Foundation for Res. and Education, P.O. Box 28147, San Antonio, Tex. 78284); Heberling, R. L.; Smith, G. C.; Helmke, R. J. *J. Natl. Cancer Inst.* 55(3):735; 1975. (8 references)

2437 CELLULAR RECEPTORS OF THE IMMUNE SYSTEM. (Rus.) Galaktionov, V. G. (N. I. Pirogov Second Moscow State Medical Inst., U.S.S.R.). *Usp. Sovrem. Biol.* 80(1):84-101; 1975. (126 references)

2438 HOW CANCER AND THE FETUS ELUDE THE IMMUNE DEFENSE. (Fre.) Gallois, J.-M. (No affiliation given). *Recherche* 6(54):268-269; 1975. (10 references)

2439 DIFFUSE NESIDIOBLASTIC HYPERPLASIA OF THE PANCREATIC ISLETS IN INFANTILE HYPOGLYCEMIA SYNDROME. (Ger.) Kloppel, G. (Pathologisches Institut der Universitat, 2 Hamburg 20, Martinistr. 52, West Germany); Seifert, G. *Dtsch. Med. Wochenschr.* 100(38):1906-1910; 1975. (43 references)

2440 CERTAIN NOTABLE CLINICAL ATTRIBUTES OF THE HISTIOCYTIC SARCOMAS OF THE CENTRAL NERVOUS SYSTEM. (Eng.) Adams, R. D. (Massachusetts General Hosp., Boston, Mass. 02114). *Acta Neuropathol. [Suppl.] (Berl.)* 6:177-180; 1975. (6 references)

2441 PRIMARY LYMPHORETICULOSES OF THE NERVOUS SYSTEM IN ANIMALS. (Eng.) Koestner, A. (Dept. Veterinary Pathobiology, Ohio State Univ., 1925 Coffey Road, Columbus, Ohio, 43210). *Acta Neuropathol. [Suppl.] (Berl.)* 6:85-89; 1975. (10 references)

2442 TREATMENT OF FAMILIAR POLYPOSIS OF THE COLON. (Swe.) Axemo, P. (Sahlgrenska Hosp., S-413 45 Goteborg, Sweden); Darle*, N.; Garellick, G.; Larsson, A.; Nilsson, L. *Lakartidningen* 72(36):3301-3304; 1975. (19 references)

2443 CLINICAL CLASSIFICATION AND EVOLUTION OF INTESTINAL LYMPHOMAS. (Fre.) Rambaud, J. C. (Clinique de Gastroenterologie, Hopital St.-Lazare, 107, rue du Fauborg,Sains Denis, 75010 Paris, France); Tursz, T.; Matuchansky, C. *J. Med. Liban.* 28(2):193-201; 1975. (35 references)

2444 FACTORS WHICH MAY PREDISPOSE TO LYMPHORETICULAR MALIGNANCIES. (Eng.) Vianna, N. J. (Cancer Control Bureau, New York State Dept. Health, Albany, N.Y.). In: *Lymphoreticular Malignancies: Epidemiologic and Related Aspects.* Baltimore, University Park Press, 1975, pp. 111-133. (93 references)

2445 THE CLASSIFICATION OF ACUTE LEUKAEMIA. (Eng.) Clein, G. P. (Dept. Medicine, Univ. of Cambridge, England). In: *Reviews in Leukaemia and Lymphoma, 1--Advances in Acute Leukaemia* edited by Cleton, F. J.; Crowther, D.; Malpas, J. S. Amsterdam, North Holland Publishing Co., 1974, pp. 51-67. (48 references)

2446 ACUTE LYMPHATIC LEUKAEMIA IN CHILDHOOD. (Eng.) Vianna, N. J. (Cancer Control Bureau, New York State Dept. Health, Albany, N.Y.). In: *Lymphoreticular Malignancies: Epidemiologic and Related Aspects.* Baltimore, University Park Press, 1975, pp. 79-95. (46 references)

2447 ON THE EPIDEMIOLOGY OF LEUKAEMIA. (Eng.) Clemmesen, J. (Danish Cancer Registry, Inst. for Cancer Epidemiology, Copenhagen, Denmark). In: *Reviews in Leukaemia and Lymphoma, 1--Advances in Acute Leukaemia* edited by Cleton, F. J.; Crowther, D.; Malpas, J. S. Amsterdam, North Holland Publishing Co., 1974, pp. 1-50. (287 references)

2448 OESOPHAGEAL CANCER IN CHINA. (Eng.) Anonymous. *Br. Med. J.* 3(5975):61, 1975. (12 references)

2449 EXCESS BLADDER CANCER IN BEAUTICIANS [letter to editor]. (Eng.) Menkart, J. (Clairol, 2 Blachley Road, Stamford, Conn. 06902). *Science* 190(4210):96-98; 1975. (No references)

2450 CELL SURFACE PROTEIN: NO SIMPLE CANCER MECHANISMS. (Eng.) Kolata, G. B. (No affiliation given). *Science* 190(4209):39-40; 1975. (No references)

2451 ARE LYSOSOMAL ENZYMES INVOLVED IN REGULATION OF CELL PROLIFERATION? (Ger.) Seelich, F. (Institut fur Krebsforschung der Universitat Wien, Wien, Austria). *Oesterr. Z. Onkol.* 2 (2/3):31-37; 1975.

2452 CHEMICAL INDUCTION OF SPERM ABNORMALITIES IN MICE. (Eng.) Wyrobek, A. J. (Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada); Bruce, W. R. *Proc. Natl. Acad. Sci. USA* 72(11):4425-4429; 1975.

The sperm of (C57BL x C3H)F_1 mice were examined 1, 4, and 10 wk after a subacute treatment (five consecutive days, daily ip injections) with one of 25 chemicals at two or more dose levels. The fraction of sperm that were abnormal in shape was elevated above control values of 1.2-3.4% for methyl methanesulfonate, ethyl methanesulfonate, griseofulvin, benzo[*a*]pyrene, tris(2-methyl-1-aziridinyl)phosphine oxide, tris(1-aziridinyl)phosphine sulfide, mitomycin C, myleran, vinblastine sulphate, hydroxyurea, 3-methylcholanthrene, colchicine, actinomycin D, imuran, cyclophosphamide, 5-iododeoxyuridine, dichlorvos, aminopterin, and trimethylphosphate. Dimethylnitrosamine, urethane, DDT [1,1,1-trichloro-2,2-bis (*p*-chlorophenyl)ethane], 1,1-dimethyl-hydrazine, caffeine, and calcium cyclamate did not induce elevated levels of sperm abnormalities. The results suggest that sperm abnormalities might provide a rapid inexpensive mammalian screen for agents that lead to errors in the differentiation of spermatogenic stem cells *in vivo* and thus indicate agents that might prove to be mutagenic, teratogenic, or carcinogenic.

2453 MUTATIONS TO AZAGUANINE RESISTANCE INDUCED IN CULTURED DIPLOID HUMAN FIBROBLASTS BY THE CARCINOGEN, *N*-ACETOXY-2-ACETYLAMINOFLUORENE. (Eng.) Maher, V. M. (Michigan Cancer Found., Detroit); Wessel, J. E. *Mutat. Res.* 28(2): 277-284; 1975.

The ability of *N*-acetoxy-2-acetylaminofluorene (N-AcO-AAF) to induce mutations to azaguanine resistance in diploid human fibroblasts was quantitatively investigated. Male diploid cells in thymidine-hypoxanthine-aminopterin culture medium were plated in dishes, allowed to attach, and exposed to 1-10 mM N-AcO-AAF for four hours. Following exposure to the carcinogen, the medium was replaced with fresh culture medium and sufficient time allowed for three cell divisions to occur in order to overcome phenotypic lag of cellular expression of azaguanine resistance by diluting out of hypoxanthine(guanine) phosphoribosyltransferase. A parallel series of cytotoxicity experiments was set up to determine the number of viable cells per dish for each dose of N-AcO-AAF. The cytotoxic and mutagenic effect of exposure to N-AcO-AAF was clearly dose-dependent. The killing action followed single hit kinetics and the mutagenic action was directly proportional to the number of mean lethal events per cell. Mutant clones resistant to azaguanine (2.10^{-5}M) retained normal sensitivity to N-AcO-AAF and also retained the mutant phenotype over several generations in the absence of azaguanine. These results strengthen the correlation between carcinogenicity and mutagenicity of N-AcO-AAF and imply that somatic mutations by such a carcinogen could ultimately be involved causally in the carcinogenetic process.

2454 ACUTE CYTOGENETIC EFFECT OF 2-(2-FURYL)-3-(5-NITRO-2-FURYL)-ACRYLAMIDE (AF-2, A FOOD PRESERVATIVE) ON RAT BONE MARROW CELLS *IN VIVO*. (Eng.) Sugiyama, T. (Kobe Univ. Sch. Medicine, Ikuta-ku, Kobe 650, Japan); Goto, K.; Uenaka, H. *Mutat. Res.* 31(4):241-246; 1975.

The cytogenetic effects of 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide (AF-2), a food preservative used in Japan, on bone marrow cells *in vivo* were studied in male Long-Evans rats. The aberrant metaphase cells in the bone marrow increased and reached the peak level six hours after ip injection of 240 mg/kg of AF-2 and returned to the normal level within 24 hr. A dose-response relationship was obtained using 4-240 mg/kg of AF-2. Chromosome aberrations were also induced after po administration of 30-240 mg/kg. The aberrations were mostly chromatid breaks and chiasma-like interaction of sister chromatids was also observed. The results provide the first evidence of *in vivo* cytogenetic effects of AF-2 on mammalian cells and, together with the evidence of mutagenicity already proved in other organisms, warn of the possible hazards to cells exposed to this compound.

2455 MUTAGENICITY OF THE FOOD ADDITIVE AF-2, A NITROFURAN, IN *ESCHERICHIA COLI* AND CHINESE HAMSTER CELLS IN CUTURE. (Eng.) Wild, D. (Zentrallaboratorium für Mutagenitätsprüfung der Deutschen Forschungsgemeinschaft, Freiburg, i. Br., West Germany). *Mutat. Res.* 31(3):197-199; 1975.

The induction of gene mutation by the nitrofuran food additive, furylfuramide (AF-2), in streptomycin-resistant *Escherichia coli* B and in cultured V79 Chinese hamster cells was studied. (The gene mutation involved in the Chinese hamster cells was conversion from 8-azaguanine (AZG)-sensitivity to -resistance.) Expression times for newly induced mutants were based on previous observations; the times not fixed, but were adjusted to three average generations taking into account growth delays. AF-2 concentrations (two hours exposure) of 5×10^{-5} M to 1×10^{-5} M were only moderately lethal to *E. coli* with the lowest survival rate of 67%. However, at cell density lower than 10^{10} cells/ml, AF-2 showed a higher toxicity. The AZG-resistant V79 cells had an absolute plating efficiency of 86-108%. AF-2 produced a significant dose-dependant increase in AZG-resistant mutants at concentrations higher than 10^{-4} M (24% survival at 4×10^{-4} M after two hours exposure). The mutagenic efficiency of AF-2 was 1% that of *N*-methyl-*N'*-nitro-*N*-nitrosoguanine (MNNG), with AF-2 at 2×10^{-4} M and MNNG at 2×10^{-6} M showing similar mutant frequencies. These results indicate a mutagenicity of AF-2 or its metabolites for mammalian cells. More *in vivo* studies must be undertaken to elucidate the molecular mechanism(s).

2456 FLUORESCENCE IN PISTACHIO NUTS CONTAMINATED WITH AFLATOXIN. *(Eng.)* Dickens, J. W. (Agricultural Experiment Station, North Carolina State Univ., Raleigh, N.C. 27607); Welty, R. E. *J. Am. Oil Chem. Soc.* 52(11):448-450; 1975.

The possible relationship between bright greenish yellow fluorescence and aflatoxin contamination was investigated in pistachio nuts. Bright greenish-yellow fluorescence under long wave ultraviolet light was observed on the shells of 7% of the nuts in samples from 46 aflatoxin contaminated commercial lots of Iranian pistachio nuts. Kernels from the fluorescent nuts contained 50% of the aflatoxin in the samples. No aflatoxin was found in any of the shells. When kernels and shells were cultured, toxicogenic fungi grew from only 4% of the shells and 21% of the kernels from fluorescent nuts and from 9% of the shells and 15% of the kernels from nonfluorescent nuts. Bright greenish-yellow fluorescence may indicate that conditions have been favorable for growth of toxicogenic molds on these nuts.

2457 ULTRASTRUCTURAL ALTERATIONS AND MODIFICATIONS OF NUCLEAR RNA OF RAT LIVER BY THE COMBINED ACTION OF THIOACETAMIDE AND AFLATOXIN. (Eng.) Reynier, M. O. (Centre de Recherches Scientifiques sur le Cancer, B.P. N° 8, 94800 Villejuif, France); Lafarge-Frayssinet, C.; Frayssinet, C. *Int. J. Cancer* 16:488-497; 1975.

The mechanism of action of aflatoxin in the rat liver was studied at the level of RNA synthesis. Male Wistar rats were given nine daily ip injections of thioacetamide (TAA, 50 mg/kg/day), and then, one hour before sacrifice, were given a single ip injection of aflatoxin B_1 (350 μg/kg); ^{14}C-orotic acid (8 or 20 μCi) was given ip 1-2 hr before killing. Other animals were given TAA alone, aflatoxin alone, or ^{14}C-orotic acid only (controls). The incorporation of label into the hepatic nuclear RNA was determined, and the livers were examined by electron microscopy. TAA slightly inhibited nuclear RNA synthesis, while aflatoxin inhibited it by up to 45%; aflatoxin in combination with TAA produced the same results as aflatoxin treatment (from 0.27 to 0.22), while TAA treatment caused a 170% increase in this ratio. In rats treated with TAA plus aflatoxin, the nuclear RNA:DNA ratio increased above control levels but remained much lower than the value seen with TAA alone. In untreated controls, the incorporation of orotic acid into nuclear RNA did not increase between the first and second hours. In animals treated with aflatoxin, the specific activity of the nuclear RNA was much lower one hour later, and part of the RNA synthesized during the hour preceding aflatoxin B_1 injection disappeared. In the controls, the specific activity of cytoplasmic RNA increased between the first and second hours after precursor administration. Aflatoxin administration increased the labeling of cytoplasmic RNA without affecting the passage of RNA from nucleus to cytoplasm. Morphologically, aflatoxin plus TAA intensified the lesions (enlarged nuclei and nucleoli) produced by TAA alone and led to the development of clear spaces in the nucleoplasm and atypical segregations in the enlarged nucleoli. The results indicate that aflatoxin degrades nuclear RNA without unblocking the TAA-blocked maturation of ribosomal precursors while aggravating the TAA-induced morphological lesions.

2458 REDUCTION IN BINDING OF [^{14}C] AFLATOXIN B_1 TO RAT LIVER MACROMOLECULES BY PHENOBARBITONE PRETREATMENT. (Eng.) Garner, R. C. (Dept. Exp. Pathol. Cancer Res., Univ. Leeds, England) *Biochem. Pharmacol.* 24(16):1553-1556; 1975.

The binding of [^{14}C]aflatoxin B to rat liver macromolecules was investigated in control and phenobarbitone-treated animals in an attempt to clarify seemingly contradictory findings from previous studies in some of which phenobarbitone exerted a protective effect against aflatoxin B_1, and in others increased aflatoxin B_1 metabolism. Male Wistar rats were injected ip with 40 μg/100 g [^{14}C]aflatoxin B, dissolved in dimethylsulfoxide. Phenobarbitone-pretreated animals received 1 mg/ml sodium phenobarbitone in the drinking water for seven days prior to carcinogen administration. Animals were killed six hours after aflatoxin administration, and the liver and kidney radioactivities were determined. The percentage of [^{14}C]aflatoxin B_1 remaining in the liver and kidneys after carcinogen injection was the same for control and phenobarbitone-treated rats. In control animals, binding of carcinogen to liver nucleic acids was higher than binding to protein. Phenobarbitone treatment decreased carcinogen binding to nucleic acids so that on a per milligram basis binding to all liver macromolecules was similar. Differences were also seen in kidney macromolecular binding for the two groups of animals; there was less nucleic acid-bound carcinogen in enzyme-induced rats. Protein binding in the liver and kidney was unaffected by prior phenobarbitone administration. The decreased binding of aflatoxin B_1 to nucleic acids in phenobarbitone-induced animals suggests that induction reduces the amount of reactive carcinogen formed during metabolism by liver mixed function oxidases. This reduction in nucleic acid binding may account for the protective effect of phenobarbitone on aflatoxin B_1 toxicity and carcinogenicity. These data as well as previously published reports indicate an apparent discrepancy between *in vivo* and *in vitro* aflatoxin B_1 activation. This difference may be due to a fundamental change in the pharmokinetics of aflatoxin B_1 (more metabolism proceeding *via* detoxification pathways in the animal than in the artificial microsomal system).

2459 INDUCTION OF TUMORS OF THE URINARY BLADDER IN FEMALE MICE FOLLOWING SURGICAL IMPLANTATION OF GLASS BEADS AND FEEDING OF BRACKEN FERN. (Eng.) Miyakawa, M. (Faculty of Medicine, Kyoto Univ., 53 Shogoin-kawaramachi, Sakyo-ku, Kyoto 606, Japan); Yoshida, O. *Gann* 66(4):437-439; 1975.

The carcinogenic effect of bracken fern (*Pteris aquiline*) to the urinary bladder of mice was studied. Powdered bracken fern mixed with a basic commercial diet (1:4 by weight) was fed to a group of 40 ICR strain mice for 20 wk after the implantation of a glass bead into the bladder. The animals were observed for a total of 70 wk. Fifteen mice survived 40 or more wk and four mice (27%) developed urinary bladder tumors. No urinary bladder tumor was found in a group of mice fed a similar bracken fern diet mixture without a glass bead in their bladder and in a control group fed a normal diet after the implantation of a glass bead. The

results may indicate that there is a metabolite(s) in the urine of bracken-fed mice carcinogenic to the bladder.

2460 ABSENCE OF TOXIC AND CARCINOGENIC EFFECTS AFTER ADMINISTRATION OF HIGH DOSES OF CHROMIC OXIDE PIGMENT IN SUBACUTE AND LONG-TERM FEEDING EXPERIMENTS IN RATS. (Eng.) Ivankovic, S. (Institut für Toxicologie und Chemotherapie, Deutsches Krebsforschungszentrum, D-69 Heidelberg 1, Bundesrepublik Deutschland); Preussmann, R. *Food Cosmet. Toxicol.* 13(3):347-351; 1975.

Cr_2O_3, which as chromium oxide green (C-green 9) or pigment green 17 is used in cosmetics, was tested in BD rats for subacute toxicity (90-day test) and for long-term toxicity and carcinogenicity (2-yr study). Administration of 2 or 5% in the feed for 90 days produced no signs of toxic effect. The only striking observation was a dose-dependent reduction in the liver and spleen wt in the 90-day study. No significant histological or hematological changes were found. Fertility of the animals was normal during treatment, and the young showed no malformations. Feeding of 1, 2 or 5% Cr_2O_3 in the feed for 2 yr was well tolerated. The animals were observed throughout life and there was no reduction in the average life expectancy of the experimental animals. At the end of the 2-yr study the rats were fed control diet until they were dead or moribund. All important organs including the CNS were studied histologically. Even with the very high oral doses of Cr_2O_3 given, no carcinogenic action was detected.

2461 CARCINOMA OF THE URINARY BLADDER IN PATIENTS RECEIVING CYCLOPHOSPHAMIDE. (Eng.) Wall, R. L. (Univ. Hosp., 410 W. 10th Aven., Columbus, Ohio 43210); Clausen, K. P. *N. Engl. J. Med.* 293(6): 271-273; 1975.

The occurrence of interstitial hemorrhagic cystitis and carcinomas of the urinary bladder in five patients receiving large cumulative doses of cyclophosphamide is reported. A 47-yr-old man with multiple myeloma received 295 g total cyclophosphamide over five years; squamous-cell carcinoma of the urinary bladder developed, and death due to urinary-tract obstruction occurred at about 17 mo after the first episode of hematuria. A similar course occurred in a 63-yr-old man with IgG myeloma who had received a total dose of 114 g cyclophosphamide over three years. A 57-yr-old man with IgG myeloma had received 252 g of cyclophosphamide over five years and ten months; death was due to invasive squamous cell carcinoma of the urinary bladder. A 60-yr-old man with IgG myeloma, receiving 192 g over four years, died of undifferentiated carcinoma of the urinary bladder. The only survivor was a man in whom Hodgkin's had been diagnosed at age 27 yr. He had received 147 g of cyclophosphamide over three years, which was discontinued because of hemorrhagic cystitis. For the next 10½ yr, he received a total dose of 23 g of chlorambucil. He was then found to have epidermoid carcinoma of the urinary bladder and associated extensive *in situ* carcinoma. The following cautions are suggested by this study: discontinuance of cyclophosphamide upon hemorrhagic cystitis, intermittent use of cyclophosphamide, careful cystoscopy, and conservative use of the chemical in non-neoplastic diseases.

2462 ACETIC ACID, A POTENT STIMULATOR OF MOUSE EPIDERMAL MACROMOLECULAR SYNTHESIS AND HYPERPLASIA BUT WITH WEAK TUMOR-PROMOTING ABILITY. (Eng.) Slaga, T. J. (Fred Hutchinson Cancer Res. Center, 1102 Columbia St., Seattle, Wash. 98104); Bowden, G. T.; Boutwell, R. K. *J. Natl. Cancer Inst* 55(4):983-987; 1975.

The effects of a single application of various dose levels of acetic acid or a weak tumor promoter, phorbol-12,13-ditetradecanoate, on the incorporation of tritiated thymidine (^{3}H-TDR), ^{3}H-cytidine, and ^{3}H-leucine into DNA, RNA, and protein of mouse epidermis, respectively, were determined and compared with histologic changes in the skin. Treatment of female Charles River CD-1 mice with either 500 or 833 μM of acetic acid induced a sequential and sustained stimulation of RNA, protein, and DNA synthesis, which was followed by extensive epidermal hyperplasia similar to that reported for the strong promoter and irritan 12-*O*-tetradecanoyl-phorbol-13-acetate. A dose-response relationship between the amount of acetic aci and the rate of DNA synthesis was found between the dose levels of 33 to 833 μM of acetic acid per application. The latter dose induced the maximum activation of ^{3}H-TDR into DNA at 723% of control at two days, whereas 33 μM stimulated DNA synthesis earlier and peaked at 210% of control at three hours. Phorbol-12,13-ditetradecanoate also stimulated macromolecular synthesis in a similar sequence, though to a lesser degree. No observable inflammation and only a slight hyperplastic response were noted with phorbol-12,13-ditetradecanoate. Weekly applications of 667 μM acetic acid produced a maximal tumor response of 0.73 papilloma/mouse after 32 wk of promotion. However, a weekly dose of 677 μM acetic acid was essentially inactive when given in two divided doses. When croton oil was administered twice weekly at a 0.25%-dose level, 10.2 papillomas/mouse were induced after 32 wk of promotion. The results showed that acetic acid previously considered a nonpromoting inflammatory agent, must be a weak promote However, there was no correlation between stimulated macromolecular synthesis or hyperplasia and tumor promotion when phorbol esters were compared with acetic acid.

2463 THE MECHANISM OF CARCINOGENIC ACTION OF 1,2-DIMETHYLHYDRAZINE (SDMH) IN RATS. (Eng.) Pozharisski, K. M. (Prof. N. N. Petrov Res. Inst. Oncol., Leningrad, USSR); Kapustin, Yu. M.; Likhachev, A. J.; Shaposhnikov, J. D. *Int. J. Cancer* 15(4):673-683; 1975.

The radioactivity levels in blood, bile, urine and contents of parts of the gastrointestinal tract were studied after sc administration of ^{3}H-1,2-dimethylhydrazine (^{3}H-SDMH) (which induces colonic tumors) i 120 random-bred albino rats. The alkylation of DNA, RNA and protein in the intestinal mucosa, liver and

idneys was estimated one hour to 28 days after H-SDMH treatment from the ^{3}H-incorporation into hese macromolecules. Administration of ^{3}H-1,2-dithylhydrazine (^{3}H-SDEH) (which does not induce ntestinal tumors) was made as a control. Fifteen to 0 min after ^{3}H-SDMH treatment, marked radioactivity as found in blood, bile, urine and in contents of 11 regions of gastrointestinal tract. After ^{3}H-DMH administration, no label occurred in the conents of localized segments of gastrointestinal tract, lthough it was present in blood, bile and urine. H-SDMH methylated DNA, RNA and proteins of intestial mucosa, liver and kidney to a high degree. One our after ^{3}H-SDMH treatment, the incorporation of abel into protein of intestinal mucosa was higher han into liver and kidneys. ^{3}H-SDEH did not alkyate macromolecules in these organs, but did so in hymus, spleen and brain, which are target organs or this carcinogen. After total hepatectomy, ^{3}H-DMH did not methylate macromolecules of this intesinal mucosa. The following mechanism for the carinogenic effect of SDMH is suggested. A carcinoenic metabolite of SDMH forms, in the liver, a conugate with glucuronic acid. This glucuronide enters he gut both with bile and directly *via* the circulaion. Microbial β-glucuronidase releases the active etabolite which, in turn, alkylates tissue macroolecules.

464 BIOCHEMICAL CHARACTERIZATION OF CARCINOGEN-INDUCED MAMMARY HYPERPLASTIC ALVEOLAR NODLE AND TUMOR IN THE RAT. (Eng.) Dao, T. L. (Dep. east Surg., Roswell Park Mem. Inst., Buffalo, N. .); Sinha, D.; Christakos, S.; Varela, R. *Cancer es.* 35(5):1128-1134; 1975.

ormone responsiveness was studied in the normal ammary gland, the hyperplastic alveolar nodule (HAN) nduced by 7,12-dimethylbenz(a)anthracene (DMBA), nd the mammary tumors in Sprague Dawley female rats 55-60 days old at tumor induction). The nodules HAN) were identified, using dark-field illumination, s solid specks with no visible lobular structure. his technique was proven to be accurate by microcopic examination of stained sections. Tumors were nduced by an iv injection of 5 mg DMBA in an emulion, and the nodules were removed 45 days later. ammary tumors are usually palpable 60 days after arcinogen administration and were removed at a diaeter of 1.5 cm. The rate of casein synthesis was easured by incorporation of ^{32}P into tissue explants. asein synthesis and its stimulation by insulin, esrogen, prolactin, or cortisol was similar in HAN and n pregnant rat mammary gland, but mammary tumors ere not stimulated to increase casein synthesis by hese means. Presence of estrogen receptors was stuied by sucrose gradient analysis, and specificity of inding was shown by inhibition with the antiuterorophic compound nafoxidine. The number of estrogen inding sites per milligram DNA was about 90 in HAN, 70 in normal mammary gland, and 280 (characterized s 8S) and 167 (4S) in mammary tumors. Duration of NA synthesis was studied by pulse-labeling with [^{3}H]-hymidine and autoradiography after culture in medium ontaining insulin, prolactin, estradiol, and progesterone. Duration of synthesis was 20 hr in mammary gland, in HAN about 18 hr, and in mammary tumors about 10 hr. The low labeling index of HAN suggests that HAN contains nonproliferating cell populations. The results show that HAN cell populations differ from mammary gland and mammary tumor cells by their lack of response to hormonal stimulation for growth and lack of specific estradiol receptors.

2465 TEMPERATURE AND BLOOD FLOW MEASUREMENTS IN AND AROUND 7,12-DIMETHYLBENZ(*a*)ANTHRACENE-INDUCED TUMORS AND WALKER 256 CARCINOSARCOMAS IN RATS. (Eng.) Moller, U. (Finsen Lab., Finsen Inst., Strandboulevarden 49, Copenhagen, Denmark); Bojsen, J. *Cancer Res.* 35(11/Part 1):3116-3121; 1975.

In order to determine the validity of using temperature as a parameter of blood flow in tumors, temperature and blood flow measurements were compared in 7,12-dimethylbenz(*a*)anthracene-induced tumors and in Walker 256 carcinosarcomas in female Sprague-Dawley rats. Mammary tumors were induced by administration of 20 mg 7,12-dimethylbenz(*a*)anthracene po. After 3-5 mo, the tumors were 9-18 cm^3 and were mainly adenocarcinomas. Other rats were inoculated sc with 10^6 Walker tumor cells; 10-14 days after inoculation the tumors were 8-28 cm^3. Rats bearing Walker 256 carcinosarcomas died from metastases 4-6 wk after inoculation. Neither tumor was adherent to the skin, and there was no vascular connection between tumor and skin. In most of the tumor measurements, temperature transmitters with two thermistors and a magnetic microswitch were implanted. Temperature measurements were carried out in rats bearing 7,12-dimethylbenz(*a*)-anthracene-induced tumors continuously for one month, and rats bearing Walker 256 carcinosarcoma were measured for 2-4 wk. Blood flow was measured using the ^{133}Xe washout technique. A circadian rhythm of temperature was found both in 7,12-dimethylbenz(*a*)-anthracene-induced tumors (38.0-39.4 C, light and dark periods, respectively) and in Walker 256 carcinosarcomas (37.6-38.3 C, light and dark periods, respectively), with no significant difference in the temperatures of the two tumors. The temperature was lowest in periods of rest, and the temperature difference between light and dark periods was about 1 C. Both tumors had a higher temperature than the subcutis. External temperature measurements of the skin covering the 7,12-dimethylbenz(*a*)anthracene-induced tumors by thermistor probe and by thermography showed temperatures 1-2 C below the temperatures of surrounding skin areas. In the 7,12-dimethylbenz(*a*)anthracene-induced tumors, the blood flow was low (2.5 ml/100 g/min), which should correspond to a relatively small heat production, although the temperature was relatively high. Blood flow in skin overlying the tumor was high, presumably a perifocal hyperemic reaction, although the temperature was relatively low in this area. It is concluded that there is no correlation between tissue temperature and blood flow, and that it is not possible by means of the circadian temperature rhythm to distinguish between the hormone-dependent 7,12-dimethylbenz(*a*)anthracene-induced tumor and the hormone-independent Walker 256 carcinosarcoma.

2466 ON THE MECHANISM OF PROLACTIN AND ESTROGEN ACTION IN 7,12 DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY CARCINOMA IN THE RAT. II. *IN VIVO* TUMOR RESPONSES AND ESTROGEN RECEPTOR. (Eng.) Leung, B. S. (Dept. Surgery, Univ. Oregon Health Sciences Center, 3181 S.W. Sam Jackson Park Road, Portland, Oreg. 97201); Sasaki, G. H. *Endocrinology* 97(3):564-572; 1975.

In order to test the *in vivo* effect of prolactin on estrogen receptor (ER) binding capacity in tumors induced by 7,12 dimethylbenz(a)anthracene (DMBA-tumor), growth of the tumors from changes in prolactin and estrogen levels was compared retrospectively with cytoplasmic ER levels. The tumors were induced by intragastric feeding of 16 mg DMBA to 50-day-old Sprague-Dawley rats. ER values were determined only from adenocarcinomas. ER was measured using Scatchard plot analysis and/or by a technique involving the estimation of bound radioactive estradiol after 0.2 nM [2,3,6,7-^{3}H] estradiol (105 Ci/mM) had been added to aliquots of 40,000 x *g* post-mitochondria tumor supernatant. Some tumors required prolactin (2mg), some needed prolactin-estrogen (estradiol 0.01 μg; prolactin 2 mg) during their growth period and a small number were not influenced by hormonal milieu. ER was present in hormonally dependent tumors but was low or absent in hormonally-independent tumors. Deletion of hormones by endocrine ablation in the host rat resulted in tumor regression and loss of ER. Replenishment of ER and subsequent tumor growth were accomplished by injection of prolactin or prolactin-estrogen in endocrine-ablated rats but were not achieved in rats bearing tumors exposed to prolactin-nafoxidine (0.1 mg, daily). The results demonstrate that both estrogen and prolactin are essential for growth of hormonally dependent DMBA tumors. Tumor growth was also prevented when cytoplasmic ER was not replenished, indicating that ER may be an indispensable prerequisite for growth. Prolactin, independently of or cooperatively with estrogen, stimulated ER binding capacity. These results support the hypothesis that there may exist a prolactin regulatory mechanism of estrogen action at the tumor site. The interactions of estrogen and prolactin *in situ* in modulating hormonal receptor binding capacities may contribute to the overall stimulatory effect of these two hormones on DMBA tumors.

2467 INHIBITORY EFFECT OF ACTINOMYCIN D ON THE INDUCTION OF RAT MAMMARY TUMORS BY *IN VITRO* EXPOSURE TO 7,12-DIMETHYLBENZ(a)ANTHRACENE. (Eng.) Tominaga, T. (Res. Inst. Microbial Diseases, Osaka Univ., Yamada-kami, Suita, Osaka, Japan); Tei, N.; Taguchi, T.; Takeda, Y. *Cancer Res.* 35(7):1698-1701; 1975.

The inhibitory effect of actinomycin D on the induction of tumors by *in vitro* exposure of mammary glands to 7,12-dimethylbenz(a)anthracene (DMBA) was studied. Mammary tumors were induced by DMBA (25 mg/kg, iv) in female Sprague Dawley rats. Transplantation was to the back of the donor rat. When actinomycin D was given ip 24 hr before excision of the mammary glands, the number of tumors per number of grafts was 5 of 16 (31%). When actinomycin D was given 24 hr after excision of glands, the response was 14 of 20 (70%), compared to 7 of 8 (87.5%) with no actinomycin D. *In vitro* exposure of excised glands to DMBA first and then 100 or 500 μg actinomycin D/ml resulted in a response of 10 of 24 and 4 of 12 respectively. Exposure to DMBA only, gave 15 tumors per 21 grafts; similar results (60-70% response) were seen when actinomycin D was given first. This might be due to a difference in the amounts of DMBA and actinomycin D bound to the mammary glands.

2468 NEOPLASMS IN STRAINS OF SPLENECTOMIZED MICE AFTER A SINGLE 7,12-DIMETHYLBENZ[*a*]-ANTHRACENE TREATMENT. (Eng.) Akamatsu, Y. (Medical Coll. Georgia, Augusta, Ga. 30902). *J. Natl. Cancer Inst.* 55(4):893-897; 1975.

The effects of splenectomy on carcinogenesis by a single 10-mg dose of 7,12-dimethylbenz[*a*]anthracene (DMBA) given in olive oil by gavage was tested on both sexes of BTOs, C57BL/60s, C3H/HeOs, and BALB/cOs mice. The splenectomy, performed a week before the DMBA was given, did not affect physical status or the incidence of acute toxic death of animals. DMBA-treated animals developed neoplasms at a significantly higher rate than did untreated mice. Splenectomy did not influence the overall incidence of neoplasms. Tumors observed in DMBA-treated groups were of skin, forestomach, colon, liver, lung, adrenal, ovary, breast, hematopoietic-lymphoreticular system, and vascular system, depending on the strain. Splenectomy inhibited lung adenomas in BALB/cOs females and hepatomas in C57BL/60s females; splenectomy enhanced skin neoplasms in C57BL/60s and squamous cell carcinoma of the forestomach in BTOs males. Myelogenous leukemia was increased in DMBA-treated groups of all strains, but splenectomy inhibited the development of this type of lymphoma. It is suggested that the effect of splenectomy may be attributed to elimination of most target cells of DMBA, and exclusion of humoral factors of the spleen that help to perpetuate malignancy.

2469 INFLUENCE OF ALLOGENEIC EFFECT ON 7,12-DIMETHYLBENZ[*a*]ANTHRACENE CARCINOGENESIS IN MICE. (Eng.) Baroni, C. D. (Univ. Rome, Sch. Medicine, 00161 Rome, Italy); Uccini, S.; Ruco, L.; Soravito, G. *J. Natl. Cancer Inst.* 55(3):619-622; 1975.

Charles River mice either untreated or treated at birth with 7,12-dimethylbenz(*a*)anthracene (DMBA, 100 μg, sc) were given allogeneic spleen cells from adult C57BL/Cas donors. These spleen cells were given as a single injection (5 x 10^6 cells) either at birth or at seven or 14 days of age. Allogeneic treatment at birth significantly increased the incidence of DMBA-induced malignant lymphomas (50 tumor-bearing animals compared with 36 in the group treated with DMBA alone) and shortened the latency period of the tumors. The incidence of sc tumors was moderately increased (from 21 to 33) in DMBA-treated mice given allogeneic cells at seven days of age. Lung tumors appeared to be decreased (from 66 to 42) in the group given DMBA at birth and allogeneic cells 14 days later

Treatment with only allogeneic cells gave results essentially similar to those observed in untreated controls. It is suggested that the increased incidence of lymphoid tumors in mice given DMBA and allogeneic cells at birth could be due to an immunologic imbalance induced by a graft-*vs*-host reaction and that such an allogeneic effect may represent one of the earliest critical events triggering cancer growth. While the decreased incidence of lung tumors associated with allogeneic treatment at age 14 days may be explained by histoincompatability reaction, the greater incidence of sc tumors in mice given allogeneic cells one week after birth and DMBA treatment cannot be explained.

2470 THE STIMULATION OF 2-DEOXY-D-GLUCOSE TRANSPORT IN CONTROL AND VIRUS-TRANSFORMED CELLS BY ETHIDIUM BROMIDE. (Eng.) Soslau, G. (Hahnemann Medical Coll., Philadelphia, Pa. 19102); Nass, M. M. K. *J. Cell. Physiol.* 86(2/Suppl. 1/Part I):269-280; 1975.

Ethidium bromide was recently demonstrated to alter the plasma and subcellular membrane glycoproteins in control and virus transformed cells. In the present study, ethidium bromide (2 μg/ml) was tested for its effect on 2-deoxy-D-glucose transport in normal hamster kidney cells or cells transformed by the Bryan strain of Rous sarcoma virus (RSV); in normal rat liver cells or in cells either spontaneously transformed or transformed by nutritional stress; and in normal rat kidney cells or cells transformed by the Prague strain of RSV. The results show that ethidium bromide also stimulates the membrane associated process of sugar transport. The K_m of the virus-transformed cells and the ethidium bromide-treated cells was the same as that of the control cells, while the maximum velocity as compared with the control cells was significantly increased. The transport of 2-deoxy-D-glucose was inhibited by glucose, cytochalasin B, and neuraminidase, but was unaffected by variations in cell density or pH of the incubation medium. The kinetic data and the observations with the different inhibitors indicate that the mechanism for glucose transport is unaltered and that the number of transport sites increases upon viral transformation and also on exposure to ethidium bromide.

2471 INTERACTION OF Δ^5-ANDROSTENE-3β,17β-DIOL WITH ESTRADIOL AND DIHYDROTESTOSTERONE RECEPTORS IN HUMAN MYOMETRIAL AND MAMMARY CANCER TISSUE. (Eng.) Poortman, J. (Univ. Hosp., State Univ. Utrecht, Netherlands); Prenen, J. A. C.; Schwarz, F.; Thijssen, J. H. H. *J. Clin. Endocrinol. Metab.* 40(3):373-379; 1975.

Specific receptor binding of 17β-estradiol (E_2) and 5α-dihydrotestosterone (DHT) was studied in human myometrial tissue and in human mammary cancer tissue. The inhibition of binding for E_2 and DHT by E_2, testosterone (T), DHT, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S), androstenedione (A), and 5-androstene-3β,17β-diol (Adiol) was tested by dextran-charcoal separation of bound and free E_2, resp., and DHT. The percentage of binding inhibition was calculated with reference to the inhibition obtained with nafoxidine in a molar concentration ratio of 1000 for E_2 binding, and with cyproterone acetate in a molar concentration ratio of 10,000 for DHT. Receptors for both E_2 and DHT were present in all 15 samples of myometrium tested. Of 19 samples of mammary carcinoma tissue, one had no binding activity, three bound E_2, five bound DHT, and ten showed binding for both steroids. A 50% inhibition of E binding in myometrial and tumor tissue required a molar concentration ratio of 40 for Adiol, >2000 for T and DHT, and about 20,000 for DHEA. No significant inhibiting activity occurred with A up to a molar concentration ratio of 10,000 or with DHEA-S up to 40,000. With regard to DHT binding, Adiol was more active than E_2 and less active than T. Of the substances tested, Adiol was the only one which exerted a significant inhibiting influence at a molar ratio not far beyond the physiological range. This signifies that Adiol might interfere at the receptor level in the estrogenic stimulation of mammary cancer cells.

2472 GONADOTROPIN-INDUCED PROLIFERATION OF ENDOPLASMIC RETICULUM IN AN ANDROGENIC TUMOR AND ITS RELATION TO ELEVATED PLASMA TESTOSTERONE LEVELS. (Eng.) Neaves, W. B. (Southwestern Medical Sch., Dallas, Tex. 75235). *Cancer Res.* 35(10):2663-2669; 1975.

The development of gonadotropin-induced structural change in a testosterone-secreting Leydig cell tumor and its relationship to plasma testosterone levels were studied in castrate, tumor-bearing C57Bl/6J mice two hours after daily pc injections of human chorionic gonadotropin (HCG, 50 IU). Tumor cells from control animals were small, averaging less than 1.0×10^{-9} ml in volume, and were poorly differentiated, having very little smooth endoplasmic reticulum (SER) in their cytoplasm. Average plasma testosterone levels in these mice were near 1.3 ng/ml. Although a five-fold rise in plasma testosterone was measured two hours after the first HCG injection, no changes in the endoplasmic reticulum were detected at this time. After the second injection, plasma testosterone rose to only twice control levels, and cell ultrastructure was largely unchanged. Modest amounts of SER had appeared in many tumor cells after the third injection, and plasma testosterone showed a six-fold rise. Between the third and fourth injections, cell volume increased by about 70% as large accumulations of SER appeared in the cytoplasm of most cells. Plasma testosterone again rose to five times control levels. Increased cell volume and abundant SER were maintained by continuing daily injections of HCG, while the two-hour plasma testosterone response persisted at 5-6 times the control level. These findings show that a maximal elevation of plasma testosterone can occur prior to changes in the endoplasmic reticulum of Leydig tumor cells. However, they also suggest that daily repetition of the maximal functional response requires that the cells acquire large quantities of newly produced SER.

2473 CORTICAL IMPLANTATION OF HYDROCARBONS IN RATS AND MICE. (Eng.) Gershbein, L. L. (Northwest Inst. for Medical Res., Chicago, Ill. 60634); Benuck, I. *Oncology* 31(2):76-82; 1975.

Early brain changes following the cortical implantation of fragments of several carcinogenic hydrocarbons and azulene were studied in adult male BDF_1 mice and Holtzman rats. Pellets composed of crystals of azulene, 3-methylcholanthrene (MCA), 1,2,5,6-dibenzanthracene (DBA), or 9,10-dimethyl-1,2-benzanthracene (DMBA) were implanted cortically into groups of 14 rats; the hydrocarbons (1.0 mg/ml) were implanted ic in saline by trocan in groups of 12 mice. After intervals of 56 (rats) or 140 (mice) days, the animals were perfused with formalin, and the brains were examined microscopically. In some experiments, the rats were examined after intervals of 128-146 days. DMBA produced space-occupying lesions in 6 of 14 rats. The inflammatory lesions were filled with necrotic tissue and surrounded by an edematous border; several crystals of hydrocarbon were found within each lesion. The remaining rats injected with DMBA displayed non-space-occupying lesions, as did all animals treated with DBA, MCA, and azulene. The latter produced no edema or atypical cells. In the rats studied after 128-146 days, the treatment appeared to be somewhat better tolerated; 3 of the 9 animals treated with DMBA developed hemorrhagic space-occupying lesions, all other changes being non-space-occupying lesions. In contrast to the rats, the mice underwent few changes in brain anatomy after hydrocarbon treatment. Neoplasms as such were found in neither rats nor mice.

2474 ACTIVATION OF CARCINOGENIC POLYCYCLIC HYDROCARBONS IN POLYOMA-VIRUS-TRANSFORMED CELLS AS A PREREQUISITE FOR POLYOMA VIRUS INDUCTION. (Eng.) Huberman, E. (Dept. of Genetics, Weizmann Inst. of Science, Rehovoth, Israel); Fogel, M. *Int. J. Cancer* 15(1):91-98; 1975.

Studies were undertaken to determine whether or not carcinogenic polycyclic hydrocarbons can induce the synthesis of polyoma virus (PV) in inducible PV-transformed rat cell clones, and to determine if this induction requires metabolic activation of the carcinogens. In cultures of such clones, which metabolize benzo(a)pyrene (BP) to a level of 30-60% of that of normal cells, up to 10.4% of the cells were induced for PV synthesis by BP (1 μg/ml), 20-methylcholanthrene (MCA 0.1-10 μg/ml) and 7,12-dimethylbenz(a)-anthracene (DMBA 0.1-10 μg/ml). No PV induction was observed with the noncarcinogenic polycyclic hydrocarbons pyrene, chrysene, and benz(a)anthracene. A proportion of subclones, isolated from a PV-inducible clone, which metabolized 0.1 μg or less BP per 10^6 cells, proved noninducible by any of the carcinogenic polycyclic hydrocarbons BP, MCA and DMBA. However, subclones that metabolized more than 0.3 μg BP per 10^6 cells were all inducible for PV synthesis by these carcinogens. Subclones isolated from an inducible clone pretreated with BP were shown to metabolize less than 0.1 μg BP per 10^6 cells and were resistant to virus induction by the carcinogenic polycyclic hydrocarbons. Benzoflavone (3 μg/ml) which inhibits the metabolism of BP in clones metabolizing high levels of this carcinogen, prevented the induction of PV antigen and infectious virus synthesis in these clones. The data indicate a relationship between the carcinogenicity of polycyclic hydrocarbons and their ability to induce virus in the PV-transformed cells. The data also suggest that virus induction depends o metabolic conversion of these hydrocarbons into similar reactive compounds that are responsible for mali nant transformation and mutagenesis.

2475 SEROLOGIC EVIDENCE FOR CROSS-REACTING ANTI GENS IN TWO CARCINOGEN-INDUCED MURINE SARCOMAS. (Eng.) Fritze, D. (Harbor General Hosp., 1000 West Carson St., Torrance, Calif. 90509); Kern, D. H.; Waldman, S. R.; Pilch, Y. H.* *Int. J. Cancer* 15(1):116-131; 1975.

Serological methods were used to detect common tumor associated antigens in two murine sarcomas induced i female C3Hf/HeCr mice with methylcholanthrene (MC-1) and 3,4-benzo(a)pyrene (BP-1). Xenogenic and syngeneic antitumor antisera against the two sarcomas were studied using an isotopic, complement, dependent, antibody-mediated microcytotoxicity assay and an isotopic antiglobulin test for the detection of antibodies to tumor-associated antigens. Absorptior with various tissues consistently indicated that the specific activity of the antitumor antisera could be removed by absorption with MC-1 or BP-1 cells. In contrast, absorption with syngeneic normal adult tis sues, normal fetal tissues, and cells from a histogenetically unrelated tumor (a spontaneous C3H murir mammary carcinoma) failed to remove any specific activity. Both the microcytotoxicity assay and the modified antiglobulin test yielded the same major finding: the MC-1 and BP-1 sarcomas shared common cell-surface antigens that appeared to be tumor spe ific. The two techniques were similarly useful and sensitive enough for the detection of tumor-associa antigens in the carcinogen-induced sarcomas. The r sults suggest that chemically-induced murine sarcom contain both individual and common cell-surface ant gens, the latter detectable by serological methods. The common tumor-associated antigens may be related to a viral genome involed in the malignant transfor mation of chemically-induced murine sarcomas.

2476 THE NATURE OF THE DEOXYRIBONUCLEOSIDES INVOLVED IN THE BINDING OF CARCINOGENIC HYDROCARBONS TO THE DNA OF MOUSE EMBRYO CELLS. Brookes, P. (Pollards Wood Res. Station, Inst. of Cancer Res., Nightingales Lane, Chalfont St. Giles, Bucks, HP8 4SP, England); Jones, P.; Amos, J. *Int. J. Cancer* 15(6):912-917; 1975.

The DNA of C57Bl mouse embryo cells was specificall labeled in the purine moieties with (G^3H)-deoxyaden sine or in the cytosine moieties with ($5-^3H$)-deoxycytidine. Both labels were added at 0.5-1.5 μCi/ml of medium. These cells were then treated with tritiated 7-methylbenz(*a*)anthracene (7-MBA, 27 Ci/mM) benzo(*a*)pyrene [B(*a*)P, 4.2 Ci/mM]. For binding, th appropriate hydrocarbons were added to the cell cul tures three days after the initial plating, and the cells were harvested two days later. The DNA was isolated, degraded enzymatically to deoxyribonuclec sides, fractionated on a Sephadex LH20 column, and

he fractions were assayed for radioactivity. When he purines of the DNA were tritium-labeled, radioctive 7-MBA-deoxyribonucleoside and radioactive (*a*)P-deoxyribonucleoside products were obtained. o such products were found when the DNA was preabeled with 5-^{3}H-deoxycytidine. These results indiate that the purine moieties of DNA react with the etabolically activated hydrocarbon derivaties *in ivo*.

:477 METABOLISM OF MONOHYDROXYBENZO(a)PYRENES BY RAT LIVER MICROSOMES AND MAMMALIAN CELLS N CULTURE. (Eng.) Wiebel, F. J. (Natl. Cancer Inst. ethesda, Md. 20014). *Arch. Biochem. Biophys.* 68(2):609-621; 1975.

n vitro studies of the metabolism of 3-, 6-, and 9-onohydroxybenzo(a)pyrenes (3-, 6-, and 9-OH-BP) by icrosomes from Sprague-Dawley rat liver, both unreated and 3-methylcholanthrene (MC)-treated, were erformed. The amount of 3-, 6-, and 9-OH-BP was easured by its fluorescence at specified wavelengths. he metabolism of 3-OH-BP requires NADPH (0.5 μM). t was inhibited by carbon monoxide; in air with MCreated microsomes, 0.253 nM/mg protein/min of 3-OHP was metabolized, while in CO:O_2, 0.196 nM/mg protein/min was used. This inhibition suggests the nvolvement of a mixed function oxygenase. The metaolism of 3-OH-BP and the hydroxylation of benzo(a)yrene (BP) appear to be similar because the reaction ates were similar; both activities were induced by -MC *in vivo* treatment of rat liver microsomes 40 mg/kg); and because both MC-induced activities ere inhibited by 7,8-benzoflavone, while constituive activities were unaffected. Using ^{3}H-3-OH-BP o examine the products of microsomal metabolism by igh pressure liquid chromatography, a product cochroatographing with 3,6-quinone-BP was found. In hamter embryo cell cultures, 3-OH-BP was converted by different mechanism from that in hepatic microomes in that the phenol disappearance proceeded naffected by specific inhibitors or inducers. It is oncluded that hydroxybenzo(a)pyrenes in microsomes re metabolized by mixed-function oxygenases that re similar to BP hydroxylases.

:478 A FLUOROMETRIC STUDY OF DNA-BOUND BENZO-[a]PYRENE. (Eng.) Kodama. M. (Natl. Canr Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo, apan); Nagata, C. *Biochemistry* 14(21):4645-4650; 975.

omparisons were made among the fluorescence spectra f DNA-bound benzo[*a*]pyrene, which were produced *in ivo* and *in vitro*. DNA from skin of female ddN mice reated topically with 1.5 mg benzo[*a*]pyrene had a aximum emission beyond 400 nm, which was clearly istinguished from that of DNA-bound benzo[*a*]pyrene ,5-oxide i.e., from that of the K-region epoxide. he emission spectra from mouse skin were classified nto two groups: type I and type II. The former was imilar to the spectrum of benzo[*a*]pyrene, although he two maxima were shifted to longer wavelengths (410 and 435 nm). Type II was characterized by a road peak around 430 nm. Type I and type II were btained from different fractions of hydroxylapatite chromatography, but type I changed into type II during storage. This suggests that type II is a modified product of type I. Type I and type II were also produced in ethanol solutions (33% and 100% ethanol) of DNA irradiated for six hours by the visible light of a high-pressure mercury lamp (200 V, 1.5 A), or treated with iodine (5 mM) or hydrogen peroxide. The type II spectrum of mouse DNA resembled that produced by hydrogen peroxide, rather than that produced by iodine. Treatment of *Escherichia coli* with benzo-[*a*]pyrene (10 mg/10 ml dimethyl sulfoxide) produced only type I fluorescence. Although the relationship between types I and II remain to be established, the emission spectrum of mouse DNA indicated that the DNA-bound benzo[*a*]pyrene possessed the intact, conjugated ring structure of the parent compound. This suggests that hydroxylation by the substitution reaction at the 6,3,1 region of benzo[*a*]pyrene is responsible for the binding of benzo[*a*]pyrene to DNA. Although a cation radical cannot be excluded, it is concluded that the proximate (active) form of benzo-[*a*]pyrene is probably an hydroxylated product including an oxy radical.

2479 FACTORS AFFECTING THE QUANTITATION OF DOSE-RESPONSIVE CURVES FOR MUTATION INDUCTION IN V_{79} CHINESE HAMSTER CELLS AFTER EXPOSURE TO CHEMICAL AND PHYSICAL MUTAGENS. (Eng.) Fox, M. (Christie Hosp., Manchester M20 9BX, Great Britain). *Mutat. Res.* 29(3):449-466; 1975.

Using four common mutagens; ethyl methanesulfonate (EMS), methyl methanesulfonate (MMS), UV-irradiation, and X irradiation; the relationship between dose of mutagen, cellular lethality, and frequency of 8-azaguanine-resistant (azg^r) colonies in V79 Chinese hamster cells was studied. After exposure to mutagen, the cells were incubated for up to 120 hr before the addition of 8-azaguanine (30 μg/ml) for determination of expression times. Reconstruction experiments were performed to determine the overall cell density that interferes with mutant recovery, and determinations were made of the incorporation of [^{14}C]hypoxanthine into cultures at different cell densities. Induced mutant frequences were assayed by two methods *in situ* and after replating. After exposure to X-rays, MMS, and UV, a significantly higher frequency of mutants was observed in the replated cultures as compared with the *in situ* assays; similar observations were made at all survival levels. With EMS, an increment on replating was observed only at high survival levels. The replating data suggest that two types of azg^r colonies are produced: those containing only azg^r cells; and those that, due to damage segregation, contain a mixture of azg^r and 8-azaguanine-sensitive cells. These mixed colonies appear to be lost by metabolic cooperation when mutation frequencies are assayed *in situ*. The proportion of mixed colonies to homogenous colonies differed with different mutagens. Taking into account such factors, EMS and UV irradiation were similarly mutagenic at a given survival level, but at equitoxic doses, fewer mutants were recovered after exposure of V79 cells to MMS and X-rays. In the case of EMS, there appears to be a component of "mutational" damage that is unrelated to cell lethality and therefore probably unrelated to chromosome damage.

2480 CARCINOGEN-INDUCED DNA REPAIR IN NUCLEOTIDE-PERMEABLE *ESCHERICHIA COLI* CELLS: INDUCTION OF DNA REPAIR BY THE CARCINOGENS METHYL AND ETHYL NITROSOUREA AND METHYL METHANESULFONATE. (Eng.) Thielmann, H. W. (Institut fur Biochemie, Deutsches Krebsforschungszentrum Heidelberg, D-6900 Heidelberg 1, Im Neuenheimer Feld 280, Federal Republic of Germany); Vosberg, H.-P; Reygers, U. *Eur. J. Biochem.* 56(2):433-447; 1975.

DNA excision repair of ether-permeabilized (nucleotide-permeable) cells of *Escherichia coli* was investigated after exposure to *N*-methyl-*N*-nitrosourea (MeNOUr), *N*-ethyl-*N*-nitrosourea (EtNOUr) and methyl methanesulfonate ($MeSO_2OMe$), which are known to bind covalently to DNA. These cells, which had been pretreated with 2 ml diethylether, exhibited this repair after being treated with a 15-fold molar excess (over DNA nucleotides) of one of the carcinogens. Defect mutations in genes *uvrA, uvrB, uvrC, recA, recB, recC* and *rep* did not. Enzymic activities involved in this repair were identified by measuring size reduction of DNA, DNA degradation to acid-soluble nucleotides and repair polymerization. In permeabilized cells, methyl and ethyl nitrosourea induced endonucleolytic cleavage of endogenous DNA, as determined by size reduction of denatured DNA in neutral and alkaline sucrose gradients. An enzymic activity from *E. coli* K-12 cell extracts was purified (greater than 2,000-fold) and was found to cleave preferentially methyl nitrosourea-treated DNA and to convert the methylated supercoiled DNA duplex (RF I) of phage ΦX174 into the nicked circular form. Degradation of alkylated cellular DNA to acid solubility was diminished in a mutant lacking the 5'→3'exonucleolytic activity of DNA polymerase I, but was not affected in a mutant that lacked the DNA polymerizing but retained the 5'→3'-exonucleolytic activity of DNA polymerase I. An easily measurable effect is carcinogen-induced repair polymerization, making it suitable for the detection of covalent binding of carcinogens and potentially carcinogenic compounds.

2481 INDUCTION OF MOUSE LUNG ADENOMAS BY AMINES OR UREAS PLUS NITRITE AND BY N-NITROSO COMPOUNDS: EFFECT OF ASCORBATE, GALLIC ACID, THIOCYANATE, AND CAFFEINE. (Eng.) Mirvish, S. S. (Univ. Nebraska Medical Center, Omaha, Nebr. 68105); Cardesa, A.; Wallcave, L.; Shubik, P. *J. Natl. Cancer Inst.* 55(3):633-636; 1975.

Preliminary studies investigating the usefulness of sodium ascorbate (NaASC) and gallic acid for blocking *in vivo* nitrosation are presented. The effects of varying the concentrations of three N-nitroso compounds and $NaNO_2$ concentration in morpholine plus $NaNO_2$ and methylurea plus $NaNO_2$ systems were also studied. Groups of 40 male strain A mice were given N-nitroso compounds in drinking water; all other chemicals were added to food. Beginning at ten weeks of age, the mice were treated five days a week for 20 wk, except the groups that received methylnitrosourea, which were treated for ten weeks. Sodium ascorbate (NaASC) at the highest level tested (11.5 or 23 g/kg food) gave 89-98% inhibition of adenoma induction by the $NaNO_2$ plus piperazine, morpholine, and methylurea systems. In seven groups, NaASC produced increases of 15-59% in adenoma induction by nitrosomorpholine (NM) and mononitrosopiperazine (MNP), possibly because the mice consumed more of the nitrosamine solution. Adenoma induction by morpholine plus $NaNO_2$ was strongly inhibited by gallic acid, moderately inhibited by caffeine, and unaffected by thiocyanate. Gallic acid inhibited or had no affect on the action of NM and MNP. The proposal that NaASC (or perhaps gallic acid) be administered with readily nitrosatable drugs was discussed.

2482 MODIFICATION OF DIETHYLNITROSAMINE LIVER CARCINOGENESIS WITH PHENOBARBITAL BUT NOT WITH IMMUNOSUPPRESSION. (Eng.) Weisburger, J. H. (Natl. Cancer Inst., Building 37, Room 3B-27, Bethesda, Md. 20014); Madison, R. M.; Ward, J. M.; Viguera, C.; Weisburger, E. K.* *J. Natl. Cancer Ins* 54(5):1185-1188; 1975.

The effect of phenobarbital (PB) on the frequency of diethylnitrosamine (DENA)-induced hepatomas and on host immunologic competence was studied in 203 male Fischer rats. The rats were divided into eight groups (25-30 rats per group) and the experiment was conducted for up to 20 wk. DENA (40 ppm) was administered in drinking water. PB was added to the diet at 500 ppm, and hydroxyurea (HU, 250mg/kg) was given five times per week. Gamma fraction of antilymphocytic serum (ALG) was given in 2-ml doses during the fifth week, plus 0.5 ml per week during wk 6-20. In a group given DENA for ten weeks, 22 of 23 rats developed hepatomas, with nine total metastases. Concurrent feeding of DENA and PB for the same length of time produced cancer in 17 of 22 rats, with two metastases. The rats fed DENA and HU had a tumor incidence of 23 out of 25, with six metastases. A brief regimen of DENA for four weeks, followed by a 16-wk observation period, led to tumors in 4 of 30 rats, with no metastases. The group fed DENA for four weeks followed by PB for 16 wk had a tumor incidence of 19 out of 30, without metastases. The rats fed DENA for four weeks followed by PB for 16 wk and HU during the fifth to tenth week had a tumor incidence of 13 of 24, with no metastases. Those fed DENA for four weeks followed by ALG for 16 wk had a tumor incidence of 6 out of 24, with one metastasis. None of the rats given PB for 16 wk developed tumors. Thus, PB given together with DENA reduced the severit of carcinogenesis, but when administered after DENA it enhanced carcinogenesis. Hydroxyurea and ALG had no effect on this enhancement.

2483 INDUCTION OF PANCREATIC NEOPLASMS BY 2,2'-DIOXOPROPYL-N-PROPYLNITROSAMINE. (Eng.) Pour, P. (Univ. Nebraska Medical Center, 42nd and Dewey Ave., Omaha, Nebr. 68105); Althoff, J.; Kruger, F.; Schmahl, D.; Mohr, U. *Cancer Lett.* 1(1):3-6; 1975.

The carcinogenicity of another derivative of di-*n*-propylnitrosamine was studied. A high incidence of pancreatic duct adenomas and carcinomas were

duced in Syrian golden hamsters as early as 13 after chronic administration of 2,2'-dioxopropyl-propylnitrosamine (DOPN, sc, 10 mg/kg/wk). Pan-eatic adenomas were found in 17% of females and of males with average latencies of 18 and 15 wk spectively. Carcinomas were found in 16% and 6% females and males, respectively. Males died ur wk earlier than females on the average; their erage wt was 74 g at death compared to 105 g r females. In contrast to another pancreatic rcinogen, 2,2'-dihydroxy-propyl-*n*-propylnitros-ine, DOPN induced no tumors of the upper respir-ory tract or kidneys, and only a few neoplasms the lungs and liver.

84 *IN VITRO N*-NITROSODIMETHYLAMINE FORMATION BY SOME BACTERIA. (Eng.) Hashimoto, S. akult Inst. Microbiological Res., Tokyo, Japan); wai, Y.; Mutai, M. *Infect. Immun.* 11(6):1405-1406; 75.

cteria isolated from the feces of humans, sheep, and boratory rats were tested for the ability to cata-ze the formation of *N*-nitrosodimethylamine (*N*-DNA) om dimethylamine and nitrate. Bacteria tested in-uded strains of *Escherichia coli*, *Proteus*, *Kleb-ella*, *Clostridium*, *Pseudomonas*, *Lactobacillus*, *reptococcus*, *Veionella*, *Bacteroides*, *Propionibac-rium*, *Bifidobacterium*, *Peptostreptococcus*, *Eubac-rium*, *Ruminococcus*, and *Actinomyces*. Sixty bac-rial strains were incubated anerobically, and the lture broths were used for extraction and determin-ion of *N*-NDA. A coiled glass column packed with romosorb W-25% PEG 6000 was employed for the anal-es. The following strains were capable of cata-zing the formation of N-NDA: human pathogenic *E. li* H-140, H-146, H-158, *Pseudomonas aeruginosa*, *ebsiella pneumonia*, *Proteus mirabilis* E, *Proteus lgaris*, *Clostridium perfringens* M-1, *Proteus mira-lis*, *Proteus morganii* MM-13, *Pseudomonas* sp. nov, *ostridium* GT-127, and *E. coli* N-1, MM-32. In con-ast, some species of *E. coli* and *Proteus* isolated om the feces of human and rats failed to exhibit ch activity, as did all bacteria that were continu-ly inhibiting and predominant in the intestine of mans, rats, and sheep. It is thus suggested that cteria capable of forming *N*-DNA may be either ab-rmal or only occasional intestinal bacteria.

85 CHANGES IN PEPSINOGEN ISOZYMES IN STOMACH CARCINOGENESIS INDUCED IN RATS BY *N*-METHYL-NITRO-*N*-NITROSOGUANIDINE. (Eng.) Furihata, C. nst. Medical Science, Univ. Tokyo, Minato-ku, kyo, Japan); Sasajima, K.; Kazama, S.; Kogure, K.; vachi, T.; Sugimura, T.; Tatematsu, M.; Takahashi, *J. Natl. Cancer Inst.* 55(4):925-930; 1975.

anges in the isozymes of pepsinogen (Pg) separated om the glandular stomachs of male Wistar rats were udied by polyacrylamide gel electrophoresis during rcinogenesis induced by *N*-methyl-*N'*-nitro-*N*-nitro-guanidine (MNNG, 85 μg/ml of drinking water), from e beginning of MNNG administration to three months ter the end of the seven month regimen. In 13 of rats killed successively, one (Pg 1) of the three pepsinogen isozymes (Pg 1, 3, 4) normally present in the pyloric mucosa had decreased or disappeared. Its decrease was observed from one wk after the beginning of MNNG treatment to at least three mos after the end of the seven month MNNG administration. Remarkable histopathologic changes were found from 8 months after MNNG was given, and rats showing such unusual histo-pathologic alterations also had changes in their pepsinogen isozyme pattern. In four of 27 rats, two (Pg 1, 2) of the four isozymes of pepsinogen (Pg 1-4) in the fundic mucosa decreased or disappeared from three mo after the beginning of MNNG treatment to at least 2 months after the end of its seven month admin-istration. Histopathologic changes induced by MNNG were not as remarkable in the fundic mucosa as in the pyloric mucosa. The close relationship between his-topathologic changes in the pyloric mucosa and changes in pepsinogen isoenzyme patterns suggests that pep-sinogens may mediate the presence of a nonreversible phenotypic change related to the carcinogenic process.

2486 A STUDY OF TOBACCO CARCINOGENESIS. XIV. EFFECTS OF *N'*-NITROSONORNICOTINE AND *N'*-NITROSONANABASINE IN RATS. (Eng.) Hoffmann, D. (American Health Foundation, Valhalla, N.Y. 10595); Raineri, R.; Hecht, S. S.; Maronpot, R.; Wynder, E. L. *J. Natl. Cancer Inst.* 55(4):977-981; 1975.

N'-Nitrosonornicotine (NNN) and *N'*-nitrosoanabasine (NAB) were synthesized and administered in drinking water to male Fischer rats for 30 wk (total dose, 630 mg). 1,4-Dinitrosopiperazine (DNPI) served as the positive control. By 11 mo, all surviving rats given NNN developed esophageal tumors (12/20); one had a pharyngeal tumor and three had invasive car-cinomas originating in the nasal cavity. During the same time, only 1 of 20 rats given NAB deve-loped esophageal tumors. Compared to the strong esophageal carcinogen DNPI, NNN was a moderately active carcinogen, and NAB was a weak carcinogen. Because NNN is highly concentrated in tobacco (0.3-90 ppm) these findings should be applied to the etiology of various cancers related to tobacco chewing and smoking.

2487 METABOLISM OF NITROSAMINES *IN VIVO* IV. ISOLATION OF 3-HYDROXY-1-NITROSOPYRROLI-DINE FROM RAT URINE AFTER APPLICATION OF 1-NITROSO-PYRROLIDINE. (Eng.) Krüger, F. W. (Institut für Toxicologie und Chemotherapie am Deutschen Krebs-forschungszentrum D-6900 Heidelberg Im Neuenheimer Feld 280 Federal Republic of Germany); Bertram, B. *Z. Krebsforsch.* 83(3):255-260; 1975.

The urine of nitrosopyrrolidine-treated rats was analyzed in order to elucidate the metabolic degra-dation of this substance. Male Sprague-Dawley rats (160-250 g) were injected ip with unlabeled (400 mg/kg) nitrosopyrrolidine or 2,5- and 3,4-^{14}C-nitro-sopyrrolidine (6 mg/30 μCi/kg). The urine from 96 rats was collected for 16 hr, and the urinary metab-olites were analyzed by thin-layer chromatography, gas chromatography, and mass spectrometry. The analysis showed 7% of the injected radioactivity. Some nitrosopyrrolidine was excreted unchanged, and

some (0.9%) of the radioactivity corresponded to synthetic 3-hydroxy-1-nitrosopyrrolidine. The $^{14}CO_2$ excretion was analyzed in a CO_2 exhalation apparatus in six rats. About one-third of the injected radioactivity was excreted in all forms, with over 20% in $^{14}CO_2$ form. The results show that β-hydroxylation of nitrosopyrrolidine does not occur as a minor pathway in its metabolism.

2488 INDUCTION OF NEUROGENIC TUMORS BY NITROSOTRIALKYLUREAS IN RATS. (Eng.) Lijinsky, W. (Oak Ridge Natl. Lab., P.O. Box Y, Oak Ridge, Tenn. 37830); Taylor, H. W. *Z. Krebsforsch.* 83(4): 315-321; 1975.

Four nitrosotrialkylureas were each fed to 30 male and female Sprague-Dawley rats for 50 wk in drinking water at the same molar concentration to correlate reactions *in vivo* of nitrosamides with tumor induction. Tumors of nervous origin arose after treatment with nitrosotrimethylurea (3/30), nitrosotriethylurea (7/30), nitrosomethyldiethylurea (23/30), and nitrosoethyldimethylurea (8/30). A comparison of the relative stabilities of the four nitrosoureas in aqueous solution at various pH's showed no correlation with the tumorigenicities of the compounds. It is concluded that with the exception of nitrosotrimethylurea, the nitrosotrialkylureas have a pronounced tumorigenic action in rats.

2489 INTESTINAL TUMORS IN MICE TREATED WITH A SINGLE INJECTION OF *N*-NITROSO-*N*-BUTYLUREA. (Eng.) Ward, J. M. (Natl. Cancer Inst., Bethesda, Md. 20014); Weisburger, E. K. *Cancer Res.* 35(8): 1938-1943; 1975.

The induction of intestinal tumors by *N*-nitroso-*N*-butylurea (BNU) was studied in 80 male C57Bl/6 mice, divided into four groups of 20 each. Two groups consisted of 3-wk-old mice, and the other two of 6-wk-old mice. In each age group, one group was given 75 mg/kg of BNU and the other 150 mg/kg in a single ip injection. The control group received either vehicle injection or were untreated. All mice dying after 15 wk were autopsied, and all survivors were sacrificed and autopsied at 67 wk. Intestinal tumors developed in 14 mice receiving 75 mg/kg BNU at six weeks of age, and in 17 of those receiving 150 mg/kg at six weeks. Of those receiving BNU at three weeks of age, seven of those treated with 75 mg/kg and ten of those given 150 mg/kg developed intestinal tumors. One of the untreated and four of the vehicle-treated controls also developed intestinal tumors. The tumors were seen primarily at the pyloroduodenal junction and in the anterior portion of the small intestine; a few occurred in the cecum, colon and rectum. The tumors at the junction were not very invasive and were frequently polypoid. Tumors at the other locations were invasive adenocarcinomas, which did not metastasize. Colorectal tumors were adenomas and adenocarcinomas. BNU also induced tumors of the stomach, liver, lung, and hematopoietic system. It is concluded that older mice are more susceptible to BNU-induced tumor production and that this effect is more profound at higher doses of BNU.

2490 SEQUENTIAL DEVELOPMENT OF ETHYLNITROSOUREA-INDUCED NEURINOMAS: MORPHOLOGY, BIOCHEMISTRY, AND TRANSPLANTABILITY. (Eng.) Swenberg, J. A. (Dep. Pathol. Toxicol. Res., Upjohn Co., Kalamazoo, Mich.); Clendenon, N.; Denlinger, R.; Gordon, W. A. *J. Natl. Cancer Inst.* 55(1):147-152; 1975.

Sequential evaluations were made of the morphology and biochemistry of trigeminal nerves from control and ethylnitrosourea (ENU)-exposed rats from 1 day to 6 mo of age. Distinct increases in cellularity were evident as early as 20 days after exposure to ENU. By the 63rd day of exposure *N*-acetyl-β-glucosaminidase and β-glucuronidase activities were increased 50% ($p<0.10$) and 74% ($p<0.05$) respectively. Transplantation studies were performed with grossly normal trigeminal nerves from 32-, 63-, and 91-day-old control and ENU-exposed rats. One of eight nerves from the 32-day-old ENU-exposed donors and 2 of 5 from both the 63- and 91-day-old donors developed into neurinomas (four anaplastic, one well-differentiated) at the site of transplantation. No tumors developed from nerves of controls. These results indicate that the early increases in cellularity and acid hydrolase activities represent neoplastic rather than preneoplastic changes.

2491 INDUCTION OF LEUKEMIAS AND DIGESTIVE TRACT TUMORS IN DONRYU RATS BY 1-PROPYL-1-NITROSOUREA. (Eng.) Ogiu, T. (Dep. Chem. Pathol., Natl. Inst. Hyg. Sci., Tokyo, Japan); Nakadate, M.; Odashima, S. *J. Natl. Cancer Inst.* 54(4):887-893; 1975.

The effects of continuous administration of 1-propyl-1-nitrosourea (PNU) to 109 female five-week-old Donryu rats was investigated. PNU was given in concentrations of 150, 300, and 600 ppm in drinking water for one yr. Of 36 rats surviving past the 16th week at the highest dosage, 78% developed tumors (leukemia, 53%; intestinal tumors, 22%; ear duct tumors, 11%; stomach and lienal tumors, 8%; and mammary and thymic tumor, 6%). In the 35 rats given the intermediate dose, 86% developed tumors (leukemia, 54%; intestinal tumors, 31%; stomach tumors, 14%; and mammary tumors, 11%). The lowest dosage produced tumors in 95% of 38 rats (leukemia, 64%; mammary tumors, 21%; intestinal tumors, 13%; stomach tumors, 11%). Myelocytic, myeloblastic, and lymphoblastic leukemia and erythroleukemia were seen in 58%, 23%, 2%, and 16%, resp., of 62 leukemic rats. There was no relation between incidence of each type and PNU dose. Gastrointestinal tumors were confined to the upper duodenum and stomach. The authors conclude that PNU is useful in the study of experimental rat leukemias, especially in the analysis of the target cell for various myelogenous leukemias.

2492 MUTAGENIC SELECTIVITY OF CARCINOGENIC NITROSO COMPOUNDS. I. *N*-METHYL-*N*-NITROSOURETHANE. (Eng.) Fahmy, O. G. (Chester Beatty Res. Inst., London SW3 6JB England); Fahmy, M. J. *Chem. Biol. Interact.* 10(3):141-155; 1975.

The mutagenicity of the carcinogen methylnitrosourethane (MNUr) was examined in *Drosophila* with a view

) the determination of its activity on heterochro-
ıtic loci (especially rDNA) relative to those in
ıe euchromatin. Assays were made of the yield of
ıbosomal DNA (rDNA) mutations *(bobbed:bb)* relative
) other X-chromosome recessive lethals and visibles
(l + v)] in the same male germ cells after treat-
ent with different doses (1-10 m*M*) and at various
ages in spermatogenesis. Dose dependence followed
ıe same pattern for all genic loci and germ cell
ages. In all instances, the regression of muta-
ion frequency on injected molar dose was approxi-
ıtely linear, but could better be described by a
ıadratic dose curve. In contrast, the mutagenicity
ıttern during spermatogenesis varied according to
ıe target genes. The response of the euchromatic
oci reached a peak among the earlier germ cells
robably the spermatocytes), whereas that for the
eterochromatic sites (including rDNA) was maximal
ı mature sperm. Mutagenic selectivity for rDNA
ith MNUr, as indicated by the percentage *bb*/X-
ıtations, was among the highest for the intrinsi-
ıllly reactive carcinogens (alkylating and arylating
gents). This correlates with the strong carcino-
enicity of MNUr and adds further support to the con-
ept that rDNA mutations might well be a crucial step
ı cancer initiation.

493 DAMAGE AND REPAIR OF DNA IN VARIOUS TISSUES OF THE RAT INDUCED BY 4-NITROQUINOINE 1-OXIDE. (Eng.) Cox, R. (Veterans Admin. osp., Memphis, Tenn. 38104); Irving, C. C. *Cancer es.* 35(7):1858-1860; 1975.

-Nitroquinoline 1-oxide induces pulmonary tumors
hen given sc or skin cancer when given in repeated
ocal applications. This carcinogen is absorbed by
he lung more readily than other tissues. Therefore,
comparison was made of the ability of 4-nitroquino-
ine 1-oxide (50 mg/kg, sc) to damage DNA of the li-
er, lung, and kidney in intact Holtzman rats. A
ifferential effect on DNA damage of the different
issues was demonstrated. DNA damage was detected
ı all three organs, with the lung showing the great-
st amount of damage. All three tissues were able
o repair the damaged DNA. The preferential damage
f rat lung DNA by 4-nitroquinoline 1-oxide corre-
ates with the specificity of this carcinogen to
nduce pulmonary tumors.

494 RESERPINE AND BREAST CANCER IN A RETIREMENT COMMUNITY. (Eng.) Mack, T. M. (Can-
er Surveillance Program, Edmondson Res. Bldg., 2025
onal Ave., Los Angeles, Calif. 90033); Henderson,
. E.; Gerkins, V. R.; Arthur, M.; Baptista, J.;
ike, M. C. *N. Engl. J. Med.* 292(26):1366-1371; 1975.

ı an attempt to confirm three reports suggesting a
ausal link between rauwolfia antihypertensive drugs
nd breast cancer, all cases of such cancer appear-
ng in a retirement community of about 17,000 resi-
ents, were compared with controls chosen from a ros-
er of other women in the same community. Most re-
idents use a single care facility, and patterns of
ypertension diagnosis, rauwolfia and other drug use,
nd medical-care-system patronage were abstracted
from medical records. The prevalence of recorded rauwolfia use among the controls was 20%, and that of other drug use was correspondingly high. The risk ratio for rauwolfia use was estimated to be 1.2 (95% confidence interval, 0.7-2.2). These results do not support the hypothesis that reserpine causes breast cancer.

2495 EVALUATION OF ORAL, PHARYNGEAL, LARYNGEAL AND ESOPHAGEAL CANCER RISK IN REVERSE SMOKERS OF CHUTTAS. (Eng.) Reddy, C. R. R. M. (Andhra Med. Coll., Visakhapatnam, India); Kameswari, V. R.; Chandramouli, K. B.; Prahlad, D.; Ramulu, C. *Int. Surg.* 60(5):266-269; 1975.

The effect of pure tobacco smoking, especially reverse smoking, on the development of oral, pharyngeal, laryngeal and esophageal cancers was investigated. Five hundred and twenty cancer patients were questioned about their smoking habits, chewing habits, diet, hygiene and religion. Controls were matched with patients by sex, economic status, literacy, religion, occupation and locality; 48% of the patients could be exactly age-matched. The relative risks of cancer in each site was calculated from each smoking habit. The hard palate was the most common cancer site, comprising 197 of the 520 cases; 133 of these were women. Oral cavity and oropharyngeal cancers comprised 400 cases and pharyngeal, laryngeal and esophageal cancer comprised 120 cases. Reverse smoking of chuttas gave the highest risk of hard palate cancer. This was 19.5 times the relative risk, with floor of the mouth cancer 4.8 times, gum cancer 4.6 times, and tongue cancer 4.4 times the relative risk. Cancers of the larynx and hypolarynx gave the lowest risk (0.3 times the relative risk). The hypopharynx was the only site for which smoking of chuttas in the usual way had any significance (5.7 times relative risk). There was no significance attributed to cigarette or bidi smoking for developing cancer, but these habits were rare in areas studied. When the relative risk was expressed for all smokers, smoking was significant for oral cancers of hard palate. Dental hygiene was poor in 87% of the patients and 77% of controls, and 70% of both were in the lowest socioeconomic class. This study reemphasizes the strong association between reverse smoking and cancer of the hard palate. The conventional chutta smoker runs a slight risk of oral cancer.

2496 ASBESTOS, SMOKING, AND LARYNGEAL CARCINOMA. (Eng.) Shettigara, P. T. (Dept. Preventive Medicine, Univ. Toronto, McMurrich Building, Toronto, Ontario, Canada M5S 1A8); Morgan, R. W.* *Arch. Environ. Health* 30(10):517-519; 1975.

The relationship between exposure to asbestos and laryngeal cancer was investigated. A retrospective study of 43 pairs of patients with laryngeal cancer and their matched controls examined a number of variables, including smoking, exposure to asbestos, and other occupational factors. Patients with laryngeal cancer and the controls were matched for age, sex, and place of residence. The data indicate a substantial association between asbestos exposure

and laryngeal cancer. Of the 43 laryngeal cancer patients, ten (23.3%) had previous exposure to asbestos; none of the control patients reported exposure. There was also a significantly higher proportion of smokers among the patients with laryngeal cancer (40, or 93.02%) than among controls (31, or 72.09%). Exposure to uranium, chromium, nickel, cobalt, arsenic, x-rays, and alcohol did not appear related to later development of carcinoma of the larynx. It is concluded that exposure to asbestos and cigarette smoking are potent factors in the development of this disease.

2497 METABOLISM OF CIGARETTE SMOKE CONDENSATES BY HUMAN AND RAT HOMOGENATES TO FORM MUTAGENS DETECTABLE BY *SALMONELLA TYPHIMURIUM* TA1538. (Eng.) Hutton, J. J. (Veterans Admin. Hosp., Lexington, Ky. 40507); Hackney, C. *Cancer Res.* 35(9): 2461-2468; 1975.

Nineteen fractions of whole condensate of smoke from the University of Kentucky Reference Cigarette IRI were tested for mutagenicity *in vitro* using a bacterial indicator system. As little as 25 μg of the active fractions were mutagenic toward histidine-requiring *Salmonella typhimurium* TA1538, if the condensates were incubated in the presence of ARS/Sprague-Dawley rat or human liver homogenates during treatment of the bacteria. Homogenates of lung were relatively inactive. Homogenates from livers of rats that were treated with 3-methylcholanthrene (100 mg/kg, ip) converted condensates to mutagens more efficiently than did liver homogenates from man or from normal or phenobarbital-treated (0.1% in drinking water for one week prior to sacrifice) rats. Use of homogenates from animals treated with 3-methylcholanthrene gave much more reproducible results in smoke fraction assays because larger numbers of revertants were obtained, and dose-response curves were linear over the range 25-250 μg condensate. The linear dose-response curves permitted quantitative comparison of the various fractions. The mutagenicity per milligram of basic fractions of whole smoke condensate was very high and that of neutral polycyclic hydrocarbons was very low. Because of the preferential sensitivity of the TA1538 test system to polycyclic amines and insensitivity to alkyl polycyclics, there was a poor quantitative correlation between mutagenicity and carcinogenicity, as measured by skin painting or *in vitro* cell transformation. If further development improves the sensitivity of the bacterial testing system to mutagenic derivatives of alkyl polycyclic and heteropolycyclic hydrocarbons, it may provide a convenient, rapid, quantitative, and inexpensive bioassay for the detection of potentially carcinogenic substances in tobacco smoke condensates.

2498 MOUSE SKIN TUMORIGENESIS AND INDUCTION OF ARYL HYDROCARBON HYDROXYLASE BY TOBACCO SMOKE FRACTIONS. (Eng.) Akin, F. J. (Richard B. Russell Agric. Res. Cent., Agric. Res. Serv., U.S. Dept. Agric., Athens, Ga.); Chamberlain, W. J.; Chortyk, O. T. *J. Natl. Cancer Inst.* 54(4):907-912; 1975.

The capacity of a neutral fraction of cigarette smoke condensate (CSC) to induce aryl hydrocarbon hydroxylase (AHH) activity in mouse skin was studie to determine if this is indicative of its polynucle aromatic hydrocarbon (PAH) content and tumorigenic potential. CSC was separated into acidic, basic, a neutral portions by solvent partitioning and silici acid chromatography. Tumorigenicity was determined by limited applications of both straight and reconstituted neutral fractions on the backs of 55-day-old, female ICR mice followed by a 0.2 ml applicati of 0.03% croton oil five times per week. The conce trations of phenolic metabolites in the alkali phas of AHH measurements were determined using a spectro photofluorometer with activation at 396 and 522 nm. A linear relationship between benzo(*a*)pyrene (BP) concentrations and tumorigenicity was used to deter mine which neutral fractions contained initiators. The F20 fraction was the most active, equaling 0.01 of the initiating effect of BP solution. The F22 fraction and 30% crude CSC had activity equal to 0.0025% of BP. Most of the F20 effect was accounte for in SF55. Treatment with F20 resulted in a 5-fold increase in AHH activity. Significant inducti also occurred with fractions F19, F22, F23, and F24 The enzyme-inducing effect of SF55 was as great as that of F20 from which it was derived. The activit was greatest in the 9,000 x *g* supernatant rather th in crude homogenate of epidermis. These results im ply that more potential tumorigens can be detected by measurements of the promoting activity of a give fraction than by measuring its initiation capabilit

2499 REGULATION OF ARYL HYDROCARBON [BENZO(*a*) PYRENE) HYDROXYLASE ACTIVITY IN MAMMALIAN CELLS: INDUCTION OF HYDROXYLASE ACTIVITY BY N^6, O^2 DIBUTYRYL ADENOSINE 3':5'-MONOPHOSPHATE AND AMINOPHYLLINE. (Eng.) Yamasaki, H. (Weizmann Inst. Science, Rehovot, Israel); Huberman, E.; Sachs, L. *J. Biol. Chem.* 250(19):7766-7770; 1975.

The effects of treating hamster BHK cells with N^6, O^2-dibutyryl adenosine 3':5'-monophosphate (Bt_2cAMP 1 mM), aminophylline (0.7 mM), theophylline (0.3 mM papaverine (17 μM), cyclic AMP (10 mM), or N^2O^2-dib tyryl guanosine 3':5'-monophosphate (Bt_2cGMP, 1 mM) on aryl hydrocarbon (benzo(*a*)pyrene) hydroxylase activity were investigated. The reaction mixture for hydroxylase activity contained cell homogenates (0. 2.0 mg protein) and 62.5 nM benzo(*a*)pyrene; activit was measured by a fluorometric method. RNA and protein synthesis were measured by incubating the cell for 30 min with [^{3}H]uridine (0.2 μCi/mL) or [^{3}H]leucine (1.0 μCi/ml) at 37 C. The highest increase, 100-fold, was obtained with Bt_2cAMP plus aminophyll or theophylline. N^2,O^2-Dibutyryl guanosine 3':5'-monophosphate gave a lower induction than Bt_2cAMP. The level of hydroxylase activity started to decrea six hours after treatment with the inducer and was reduced to almost the uninduced level after 24 hr. Repeated addition of Bt_2cAMP and aminophylline did not prevent this decrease. The hydroxylase could also be induced by treating cells with benz(*a*)anthra cene (8.3 μM), and the level of this induced activit was maintained for 24 hr. Aminophylline gave a 2-to 8-fold stimualtion of the induction by benz(*a*)anthra cene. The enzyme activity induced by Bt_2cAMP, amino

hylline, and benz(*a*)anthracene converted benzo(*a*)-yrene to similar alkali-extractable metabolites with fluorescence spectra similar to that of 3-hydroxy-enzo(*a*)pyrene. These induced enzyme activities also howed a similar heat stability. Induction by Bt_2-AMP and aminophylline, like induction by benz(*a*)-nthracene, required continued protein synthesis and nly an initial period of RNA synthesis. Compared to he benz(*a*)anthracene-induced hydroxylase with a K_m f 4.3 μM, the hydroxylase induced by Bt_2cAMP and minophylline showed a K_m of 0.14 μM, and was 100-fold ore sensitive to inhibition by 7,8-benzoflavone (10^{-4}-10^{7} M). Increasing the serum concentration in he culture medium stimulated the induction by amino-hylline but did not stimulate induction by benz(*a*)-nthracene. The results indicate that aryl hydro-arbon (benz(*a*)pyrene) hydroxylase can be induced by ompounds that increase the level of AMP, and that his induction and induced enzyme activity differs rom that caused by benz(*a*)anthracene.

2500 INDUCTION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY IN VARIOUS CELL CULTURES BY 2,3-7,8-TETRACHLORODIBENZO-*p*-DIOXIN. (Eng.) Niwa, A. (Natl. Inst. Child Health and Human Development, Bethesda, Md. 20014); Kumaki, K.; Nebert, D. W. *Mol. Pharmacol.* 11(4):399-408; 1975.

Hydroxylase induction by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was characterized in a number of established cell lines and primary cell cultures from various species. The established cell lines included TRL-2, ERL-2, NRKE, Chang liver, VERO, HTC, LB82, H-4-II-E, Hepa-1, MA, and E-3. Primary cell cultures were derived from fetal hamsters, rats, chickens, rabbits, and four inbred strains of mice. Cultured human lymphocytes were also studied. TCDD and/or 3-methylcholanthrene (MC) was added in varying amounts to the cultures 24 hr after plating; 24 hr later, the cultures were assayed for hydroxylase activity and protein content. The kinetics of aryl hydrocarbon (benzo(α)pyrene) hydroxylase induction by TCDD among the established lines and primary cultures was similar to the time course of hydroxylase induction by MC. The TCDD-inducible process was sensitive to actinomycin D (40 nM) and cycloheximide (350 nM or 3.5 μM). The induced enzyme activity in the cells treated with TCDD (0-100 nM) plus MC (0-10 μM) was not greater than that in cells exposed to either agent alone. There was no relationship between cytotoxicity by TCDD (1.5, 300, or 30 nM) and the level of inducible hydroxylase activity in culture. The estimated ED_{50} values for the hydroxylase induction by TCDD ranged from about 0.12 nM in C57BL/6N mouse cultures and 0.23 nM in the H-4-II-E cell line to more than 100 nM in the VERO and HTC cell lines. No hydroxylase activity was detectable in control, MC-, or TCDD-treated LB82 cells. In several cell lines and in the primary cultures, the responsiveness to TCDD was 250-900 times greater than that to MC. The responsiveness to TCDD in C57BL/6N mouse-derived cultures was about 16 times greater than that to TCDD in DBA/2N-derived cultures; this difference is similar to that previously observed in these two mouse strains *in vivo*. A bioassay with H-4-II-E cells is suggested for the detection of minute (10^{-14} M) levels of TCDD.

2501 FOREIGN-BODY TUMORIGENESIS BY VINYL CHLORIDE VINYL ACETATE COPOLYMER: NO EVIDENCE FOR CHEMICAL COCARCINOGENESIS. (Eng.) Brand, K. G. (Univ. of Minnesota Medical Sch., Minneapolis, Minn. 55455); Buoen, L. C.; Brand, I. *J. Natl. Cancer Inst.* 54(5):1259-1262; 1975.

Vinyl chloride monomers, released from implants of vinyl chloride vinyl acetate copolymer (VCA), were investigated in order to determine if they had a cocarcinogenic effect in foreign body (FB) tumorigenesis. One of the following substances was implanted into CBA/H and CBA/H-T6 mice: VCA films (2 mm thick); VCA powder equal by weight to two films; and glass films (#2 and #3 thickness). Pulverized FB was implanted ip or sc with a nebulizer dispenser. The VCA powder was implanted in 76 6-wk-old mice. Autopsy of the mice, most of which died after 30 mo, revealed no tumors that could have been unequivocally caused by VCA. Roughened VCA films were implanted in 26 mice and smooth VCA films were implanted in 53 mice. There was no increase in the rate of tumorigenesis by virtue of the increased surface area in the rough *versus* smooth implant groups. VCA films were implanted in ten female mice and for ten months, after which the implants were removed and a second VCA film was implanted in the opposite flank. There was no significant shortening of tumor latency in these animals. VCA powder, equal to four VCA films, was implanted sc into 11 mice and ip into ten mice. At eight months, single smooth VCA films were implanted in the same mice. There was no significant acceleration of tumor appearance in these animals. The results may be indicative of tumor production by FB tumorigenesis alone, and not FB/VCA cocarcinogenesis. The study also disproves the contention that tumorigenesis induced by VCA implants is due to both FB and chemical tumorigenesis. It is concluded that VCA implants are not suitable for studying this type of cocarcinogenesis.

2502 BIOLOGICAL REACTIVITY OF PVC DUST. (Eng.) Richards, R. J. (Dep. Biochem., Univ. College, Cardiff, Wales); Desai, R.; Hext, P. M.; Rose, F. A. *Nature* 256(5519):664-665; 1975.

The biological reactivity of polyvinyl chloride (PVC) dust was studied by a hemolysis technique and compared with the hemolytic potential of reactive chrysotile asbestos A; the effect of polyvinyl chloride on lung fibroblast cultures was also investigated. Two samples of PVC were tested (KM 1 and KM 2) both of which were obtained as finely-divided dried powders intended for use in fabrication work. The first sample (KM 1) was highly hemolytic at relatively low concentrations, 100% hemolysis (over 50 min) being achieved by 7.5-10 mg dust. The second sample (KM 2) was practically nonhemolytic. The sample of 100 mg of KM 2 PVC gave an equivalent hemolytic effect to 1 mg of sample KM 1. When the hemolytic activity with time of a sample of KM 1 PVC (7.5 mg) was compared with an equivalent mass of chrysotile asbestos A, the asbestos was a faster agent, although total lysis was achieved by PVC after one hour. Samples of KM 1 PVC (7.5 mg) were washed

in 3 ml veronal buffer followed by centrifugation (2,000 revolutions/min for 20 min), and the hemolytic potency of the washed dust samples and the supernatant were determined. After a single wash, the hemolytic potency was reduced by over 60%, and subsequent washes reduced the activity of the dust even further. The effect of KM 1 PVC was studied on the levels of cell mat DNA, RNA, protein and hydroxyproline in lung fibroblast cultures maintained *in vitro* for 24 days. Before addition of different concentrations of KM 1 PVC (50-200 μg/ml culture medium or 0.5-2.0 mg/culture) the dust sample was first washed in a balanced salt solution containing antibiotics. Fibroblast cultures treated with the dust all had lower levels of cell mat hydroxyproline after 24 days. There was some fluctuation in DNA levels, but little change occurred in the level of total protein or RNA. It is concluded that certain forms of PVC dusts exhibit a high hemolytic potential because of the presence of a readily soluble, surface-associated agent.

2503 EFFECTS OF VINYL CHLORIDE EXPOSURES TO RATS PRETREATED WITH PHENOBARBITAL. (Eng.) Drew, R. T. (Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Res. Triangle Park, N.C. 27709); Harper, C.; Gupta, B. N.; Talley, F. A. *Environ. Health Perspect.* 11:235-242; 1975.

Male Charles River CD-1 rats were exposed to ten consecutive days, six hours/day, to vinyl chloride vapors at an average concentration of 13,500 ppm. The exposed rats were divided into three groups of eight rats each: one group was pretreated with 3-methylcholanthrene; (15 mg/kg, ip for two days prior to first exposure); one group was pretreated with phenobarbital (1 mg/ml in drinking water for three days prior to exposure and during exposure); and the third group received no treatment. Half the animals in each group were sacrificed 18 hr after the last exposure and half were sacrificed four days later. In a second experiment, four rats pretreated with phenobarbital were exposed to vinyl chloride vapors at a concentration of 17,300 ppm for two days and sacrificed on the third day. In both experiments, control animals, also treated with phenobarbital or 3-methylcholanthrene, were exposed to air only. At the time of sacrifice, lungs, kidneys, spleen, heart, and a small piece of liver from each animal were preserved for histological examination. The remainder of the liver was processed for assay of microsomal enzyme activity. The following parameters were investigated: growth rate, organ weights, morphological changes, and both benzphetamine-*N*-demethylase activity and cytochrome P-450 content of microsomes prepared from the livers. In both experiments the only marked difference noted in any group was a decrease in the growth rate of the animals exposed to vinyl chloride and treated with phenobarbital. This decreased growth rate was particularly apparent on the third day of the vinyl chloride exposures. Occasional morphological changes were also seen in the livers of the animals treated with phenobarbital and exposed to vinyl chloride. Although changes resulting from exposure to VC and phenobarbital have been demonstrated, these changes have not been shown to be preneoplastic.

2504 UNIQUE PROPERTIES OF INBRED SYRIAN HAMSTERS FOR CARCINOGENESIS STUDIES [abstract]. (Eng.) Homburger, F. (Bio-Res. Inst., Cambridge, Mass.); Handler, A.; Laird, C. *Lab. Invest.* 32(3): 427; 1975.

2505 THE IMMUNOLOGICAL EFFECTS OF THYMECTOMY AND BCG CELL WALL SKELETON ON PRODUCTION OF LUNG CANCER IN RABBITS INDUCED BY CHEMICAL CARCINOGENS [abstract]. (Jpn.) Hirao, F. (Osaka Univ. Medical Sch., Osaka, Japan); Nishikawa, H.; Taniyama, T.; Azuma, I.; Ogura, T.; Yamamura, Y. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting,* October, 1975, p. 47.

2506 TUMOR INDUCTION BY A SINGLE SUBCUTANEOUS ADMINISTRATION OF STERIGMATOCYSTIN IN NEWBORN MICE [abstract]. (Jpn.) Fujii, K. (Sch. Med., Univ. Tsukuba, Ibakari, Japan); Kurata, H.; Odashima, S. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting,* October, 1975, p. 45.

2507 SPECIES AND STRAIN DIFFERENCES IN SUSCEPTIBILITY TO THE CARCINOGENICITY OF FLOWER STALKS OF *PETASITES JAPONICUS* MAXIM [abstract]. (Jpn.) Fushimi, K. (Gifu Univ., Sch. Medicine, Gifu, Japan); Kato, K.; Kato, T.; Matsubara, N.; Hironi, I. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting,* October, 1975, p. 45.

2508 MALONATE AS A PRECURSOR IN THE BIOSYNTHESIS OF AFLATOXINS. (Eng.) Gupta, S. R. (Vallabhbhai Patel Chest Inst., Univ. Delhi, Delhi-7, India); Prasanna, H. R.; Viswanathan, L.; Venkitasubramanian, I. A. *J. Gen. Microbiol.* 88 (2):317-320; 1975.

2509 ACTION OF WEAK BASES UPON AFLATOXIN B_1 IN CONTACT WITH MACROMOLECULAR REACTANTS. (Eng.) Beckwith, A. C. (Agric. Res. Serv., Peoria, Ill.); Vesonder, R. F.; Ciegler, A. *J. Agric. Food Chem.* 23(3):582-587; 1975.

2510 AMMONIATION OF AFLATOXIN B_1. MASS SPECTRAL ANALYSIS OF COMPOUNDS SEPARATED BY MICROSUBLIMATION. (Eng.) Stanley, J. B. (South Reg. Res. Cent., Agric. Res. Serv., New Orleans, La.); Lee, L. S.; Cucullu, A. F.; deGruy, I. V. *J. Agric. Food Chem.* 23(3):447-449; 1975.

2511 IMPROVEMENTS IN THE THIN-LAYER CHROMATOGRAPHY OF NATURAL PRODUCTS. I. THIN-LAYER CHROMATOGRAPHY OF THE AFLATOXINS. (Eng.) Heathcote, J. G. (Univ. Salford, England); Hibbert, J. R. *J. Chromatogr.* 108(1):131-140; 1975.

2512 MYCOTOXINS IN HOT SPOTS IN GRAINS. I. AFLATOXIN AND ZEARALENONE OCCURRENCE IN STORED CORN. (Eng.) Shotwell, O. L. (Northern Regional Res. Lab., Agricultural Res. Service, U.S.

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t. Agriculture, Peoria, Ill. 61604); Goulden, L.; Bothast, R. J.; Hesseltine, C. W. *Cereal em.* 52(5):687-697; 1975.

13 AFLATOXIN OCCURRENCE IN 1973 CORN AT HARVEST. I. A LIMITED SURVEY IN THE SOUTHSTERN U.S. (Eng.) Lillehoj, E. B. (Northern gional Res. Lab., Agricultural Res. Service, U.S. pt. Agriculture, Peoria, Ill. 61604); Kwolek, W. ; Shannon, G. M.; Shotwell, O. L.; Hesseltine, C. *Cereal Chem.* 52(5):603-611; 1975.

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2559 VINYL CHLORIDE DETECTION USING CARBON MONOXIDE AND CARBON DIOXIDE INFRARED LASERS. (Eng.) Freund, S. M. (Opt. Phys. Div., Natl. Bur. Stand., Wash., D.C.); Sweger, D. M. *Anal. Chem.* 47(6):930-932; 1975.

2560 UPTAKE AND PHARMACODYNAMICS OF VINYL CHLORIDE ADMINISTERED TO RATS BY DIFFERENT ROUTES [abstract]. (Eng.) Withey, R. J. (Branch of Chemical Safety, Health and Welfare, Canada, Ottawa, Ontario, Canada). *Toxicol. Appl. Pharmacol.* 33(1):146; 1975.

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* (Rev): 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2423, 2424, 2425, 2526, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2449
* (Phys): 2563, 2569, 2570
* (Immun): 2666, 2683, 2714, 2727
* (Path): 2769, 2770, 2792, 2834, 2858
* (Epid): 2893, 2905, 2910

2561 CHROMOSOMAL ABERRATIONS IN BONE MARROW OF CONTINUOUSLY IRRADIATED RATS. (Eng.)
Chlebovsky, O. (Faculty of Natural Sciences, P. J. Safarik Univ., Moyzesova 11., 04 167 Kosice, Czechoslovakia); Praslicka, M.; Chlebovska, K. *Biologia (Bratislava)* 30(6):427-433; 1975.

The effects of continuous Co^{60} irradiation (0.5-82.5 R/day) on chromosomal aberrations in the bone marrow were studied in Wistar rats. An increase in chromosomal aberrations was seen on the fifth day in animals receiving 0.5 R/day. This initial increase in chromosome aberrations was also seen at other dose levels. Up until the 30th day of treatment, the number of chromosome aberrations varied considerably, and there was no increase in aberrations despite increasing total exposure. After the 30th day, the increased aberration rates stabilized, the absolute increase being 20% at 0.5-2.5 R/day, 30% at 5-10 R/day, 35% at 20-36 R/day, 45% at 53 R/day, and 55% at 82.5 R/day. There was no appreciable increase in the number of chromosomal aberrations between the 30th and 18th days of treatment. These and other previously reported data suggest that relatively low doses of continuous radiation cause fewer chromosomal aberrations than do single larger doses, and/or that damaged chromosomes are able to recover from radiation damage.

2562 *UMBRA LIMI:* A MODEL FOR THE STUDY OF CHROMOSOME ABERRATIONS IN FISHES. (Eng.)
Kligerman, A. D. (Dept. Poultry Science, Cornell Univ., Ithaca, N.Y. 14853); Bloom, S. E.; Howell, W. M. *Mutat. Res.* 31(4):225-233; 1975.

Due to the lack of information available on the effects of various clastogenic agents on the chromosomes of fishes, an *in vivo* cytogenetics model system was developed. The central mudminnow, *Umbra limi,* was chosen for this study because of its ideal karyotype consisting of 22 large meta- and submetacentric chromosomes. Intestine, stomach, kidney, and gill tissues were found to be the most suitable for clastogenic studies. Phase contrast observations were made on the chromosomes of control mudminnows and mudminnows exposed to 325 R of X-radiation. The control rate of spontaneous chromosome aberrations was found to be low (about 0.03%). In contrast, fish exposed to 325 R of X-rays had aberrations in approximately 30% of the metaphases per fish examined. An apparent increase in clumping and a decrease in the mitotic index were also noted. It is concluded that the chromosomes of *Umbra limi* display typical responses to low level radiation exposure, and that this fish would be an ideal cytogenetics model for the study of induced chromosome aberrations in fishes.

2563 EFFECTS OF X-RAY IRRADIATION ON THE SUBSEQUENT GONADOTROPIN SECRETION IN NORMAL AND NEONATALLY ESTROGENIZED FEMALE RATS. (Eng.)
Matsumoto, A. (Juntendo Univ. Sch. Medicine, Hongo, Tokyo 113, Japan); Asai, T.; Wakabayashi, K. *Endocrinol. Jpn.* 22(3):233-241; 1975.

The effects of X-ray irradiation in intact and neonatally estrogenized female rats were investigated. Female Wistar/Tw rats were irradiated with 190 R of X-rays at ten days of age and sacrificed 4, 7 or 12 mo later. Their ovaries were histologically examined, and serum levels and pituitary contents of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were determined by radioimmunoassay. Both serum levels and pituitary contents of LH and FSH rose significantly 4 and 7 mo after irradiation, although the ovaries were markedly reduced in weight. In contrast, 12 mo after irradiation, the ovaries increased in weight and consisted mostly of polyhedral, hyperplastic interstitial cell masses, and both LH and FSH in the serum and pituitary were reduced to normal levels. These characteristic changes in the ovarian weight and histological appearance could not be observed in the similarly irradiated animals, which received daily injections of estrone for the first 30 days of postnatal life, i. e., daily injection of 50 μg for the first ten days, 100 μg for the middle ten days and 200 μg for the last ten days. Serum LH levels of the estrogenized irradiated rats at 7 or 12 mo of age did not increase, although those of FSH were significantly higher than the nonirradiated intact levels. These results indicate that a rise in the blood levels of LH and FSH may be attributed to the increase in weight and the histological changes in the ovaries of the irradiated female rats. The elevation of only FSH level may not result in the abnormal growth of the irradiated ovaries.

2564 BIOLOGICAL ALTERATIONS RESULTING FROM CHRONIC LUNG IRRADIATION. I. THE PULMONARY LIPID COMPOSITION, PHYSIOLOGY AND PATHOLOGY AFTER INHALATION BY BEAGLE DOGS OF ^{144}Ce-LABELED FUSED CLAY AEROSOLS. (Eng.) Pfleger, R. C. (Inhalation Toxicology Res. Inst., Lovelace Foundation, Albuquerque, N.M. 87115); Boecker, B. B.: Redman, H. C.; Pickrell, J. A.; Mauderly, J. L.; Jones, R. K.; Benjamin, S. A.; McClellan, R. O. *Radiat. Res.* 63(2):275-298; 1975.

Three groups of four beagle dogs inhaled a ^{144}Ce-labeled fused clay aerosol; two additional dogs per group, exposed to a stable cerium-labeled fused clay aerosol, were used as controls. At monthly intervals, one diaphragmatic lobe of each of two dogs exposed to ^{144}Ce and one control animal from each group were lavaged with isotonic saline. The recovered lavage solutions were centrifuged to isolate lung cells (mostly macrophages) and surfactant for lipid analyses. The groups were sacrificed at 2, 4 and 6 mo after exposure, when the lungs of the dogs exposed to ^{144}Ce had average cumulative radiation doses of 23, 36 and 59 krad, respectively. Chronic irradiation of the lung resulted in a progressive radiation pneumonitis which was assessed clinically and pathologically at various intervals. At sacrifice, the lungs were analyzed for ^{144}Ce and the right apical and diaphragmatic lobes were minced and lyophilized and the lipids were extracted. Total lipids from all lung samples were determined gravimetrically and individual compounds were identified, isolated and quantitated. The quantities of lipid in lung tissue

pulmonary cells and in surfactant increased as a nction of time and radiation dose. Neutral lipids terol esters and triglycerides) accounted for most the increase. These results indicate the potenal importance of pulmonary lipids in the pathogenis of radiation pneumonitis and suggest the manner which lipid changes may contribute to late-occurrg sequelae such as pulmonary fibrosis and function- alterations.

565 CARCINOMA ASSOCIATED WITH IRRADIATION OF THE IMMATURE BREAST. (Eng.) Iknayan, F. (408 South Cross, Robinson, Ill. 62454). *adiology* 114(2):431-433; 1975.

wo cases of carcinoma in hypoplastic breasts are eported. One patient was treated with radiation t age one for a birthmark adjacent to one nipple; his breast failed to develop. Adenocarcinoma in his breast was diagnosed when the patient was 28-r-old. The other patient received 3,760 roentgens o the chest and abdomen (during 4 yr, beginning at ge 11), after a tentative diagnosis of lymphoma. reast development in this patient was bilaterally inimal. Adenocarcinoma of one breast was diagnosed hen the patient was 27. These cases indicate that he immature breast is not immune to radiation carinogenesis.

566 THE INFLUENCE OF AGE AND SEX ON THE ACTIVITY RATIO OF YTTRIUM-90 TO STRONTIUM-90 N THE RAT SKELETON AFTER INCORPORATION OF STRONIUM-90. (Eng.) Stevenson, A. F. G. (Heiligenbergnstitut e.V., 7799 Heiligenberg, West Germany). *ealth Phys.* 29(2):285-290; 1975.

he influence of age and sex on the behavior and istribution of ^{90}Sr and ^{90}Y was studied in Heiligenberg albino rats. Each animal received 0.5 ml f a solution containing ^{90}Sr and ^{90}Y in radioactive quilibrium; the solution was given iv, ip, im, or sc. At various intervals thereafter, the animals vere sacrificed, and the tissues and organs were analyzed by liquid scintillation counting. The ratio of Y to Sr activity in the femora rose steeply from the time of injection, reaching a value of 1 by the end of the first day. After the first day, the ratio increased more gradually, attaining a peak of over 1.5 on about the fourth day. After day 4, the ratio declined to about 0.1 at the end of the first month, remaining constant thereafter. The ratio of Y to Sr in the skeleton was linearly related to the age of the animal, and the ratio was significantly higher in females than in males of the same age. Sex and age had an additive effect on the ratio. The Y:Sr activity ratio in the liver rose from about 10 at 0.5 hr to about 400 on the fourth day. The values in the kidney and spleen rose from 3 at 0.5 hr to 100-150 after four days, while those in the heart rose from 1.5 to 14-22. The ratio in the liver, kidney, spleen, and heart decreased with increasing age. Sex differences were apparent only for the liver, in which values for males were about 25% lower than those for females. It is postulated that estrogen might promote the transport of yttrium to its ultimate site of deposition in the bones.

2567 LATE RESULTS OF IRRADIATION OF NEWBORN MICE WITH GAMMA RAYS. IV. SUMMARY OF INVESTIGATIONS AND THE EFFECT OF SEX AND DOSE OF RADIATION ON THE EXTENT OF RADIATION-INDUCED INJURY. (Pol.) Gajewski, A. K. (00-791 Warszawa, ul. Chocimska 24, Poland); Slowikowska, M. G.; Chomiczewski, K.; Szram, S. *Rocz. Panstw. Zakl. Hig.* 26(2):263-277; 1975.

2568 STUDY, BY A SEDIMENTATION METHOD, OF THE REPAIR OF SINGLE STRAND BREAKS IN DNA OF THE REGENERATING LIVER OF γ-IRRADIATED RATS. (Rus.) Zakrzhevskaia, D. T. (Inst. Biological Physics, Acad. Sciences, Pushchino, U.S.S.R.); Gaziev, A. I. *Radiobiologiia* 15(4):593-596; 1975.

2569 TUMOR INDUCTION BY X-RADIATION AND URETHANE IN RATS [abstract]. (Eng.) Myers, D. K. (Biol. Branch, Atomic Energy Canada Ltd., Chalk River, Ontario, Canada). *Radiat. Res.* 62(3): 597; 1975.

2570 MULTICARCINOGENESIS BY URETHAN AND X-IRRADIATION [abstract]. (Eng.) Vesselinovitch, S. D. (Dep. Radiol., Med., Pathol., Univ. Chicago, Ill.); Simmons, E.; Mihailovich, N. *Radiat. Res.* 62(3):597-598; 1975.

2571 HISTOPATHOLOGIC CHANGES INDUCED IN RATS BY LOCALIZED X-IRRADIATION OF AN EXTERIORIZED SEGMENT OF THE SMALL INTESTINE. (Eng.) Sebes, J. I. (Univ. Tennessee Center for Health Sciences, 865 Jefferson Ave., Memphis, Tenn. 38163); Zaldivar, R.; Vogel, H. H., Jr. *Strahlentherapie* 150(4):403-410; 1975.

2572 MOLECULAR BASIS FOR THE MUTAGENIC AND LETHAL EFFECTS OF ULTRAVIOLET IRRADIATION, PROGRESS REPORT, 4 OCT. 1973 - 29 MAY 1974. (Eng.) Grossman, L. (Brandeis Univ., Waltham, Mass.). 11 pp., 1974. [available through National Technical Information Services, Washington, D.C. Document No. COO-3232-3]

2573 O.E.R. AND R.B.E. FOR 10 MeV ELECTRONS, AND THE TWO-COMPONENT THEORY OF RADIATION ACTION. (Eng.) Winston, B. M. (Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England); Oliver, R.; Berry, R. J. *Int. J. Radiat. Biol.* 28(2):187-190; 1975.

2574 COMPARISON OF THE CARCINOGENICITY OF ^{131}I AND ^{125}I [abstract]. (Eng.) de Ruiter, J. (Radiobiological Inst. TNO, 151 Lange Kleiweg, Rijswijk, Netherlands); van Putten, L. M.; Boorman, G. A.; Hollander, C. F. *Int. J. Radiat. Biol.* 27 (6):593; 1975.

2575 THE EFFECTS OF MILLING ON DIAMETERS AND LENGTHS OF FIBROUS GLASS AND CHRYSOTILE ASBESTOS FIBERS. (Eng.) Assuncao, J. (Graduate Sch. Public Health, Univ. Pittsburgh, Pittsburgh, Pa. 15261); Corn, M. *Am. Ind. Hyg. Assoc. J.* 36 (11):811-819; 1975.

See also:

* (Rev): 2409, 2410, 2411
* (Chem): 2459, 2479
* (Immun): 2707, 2718
* (Epid): 2897, 2902

2576 LOCATION OF SEQUENCES ON THE ADENOVIRUS GENOME CODING FOR THE 5.5S RNA. (Eng.) Pettersson, U. (Wallenberg Lab., Univ. Uppsala, Uppsala, Sweden); Philipson, L. *Cell* 6(1):1-4; 1975.

The origin of a low molecular wt virus-associated RNA (VA-RNA) was mapped by hybridization of VA-RNA to specific fragments of adenovirus type 2 DNA, obtained after cleavage with three different restriction endonucleases. VA-RNA was found to hybridize exclusively to the I-strand [strand with low buoyant density in CsCl when complexed with poly(U,G)] of a segment of the viral DNA which is located between positions 0.27 and 0.32 on the unit map of the adenovirus type 2 genome. Since VA-RNA is made in larger molar amounts than any messenger RNA, the results indicate that RNA synthesis is initiated with a very high frequency at a promotor site located within fragments *Hind*III-B and *Hpa*I-A.

2577 NUCLEOTIDE SEQUENCE HOMOLOGY BETWEEN A VIRUS-SPECIFIC 6S RNA AND VARIOUS RNA SPECIES FROM ADENOVIRUS-2-INFECTED KB CELLS. (Eng.) Ohe, K. (Hiroshima Univ. Sch. Medicine, Kasumi 1-2-3, Hiroshima 734, Japan). *Gann* 66(4):375-384; 1975.

To investigate the metabolic fate of a 6S RNA (VA-RNA), which appears in human cell lines only after infection with adenovirus, various species of RNA from KB cells at different stages of infection were tested for the presence of nucleotide sequence homologous to this RNA. RNA extracted from subcellular fractions of the cells was further fractionated by sucrose gradient centrifugation and analyzed by acrylamide gel electrophoresis or by competition against ^{32}P-labeled VA-RNA in hybridization with adenovirus DNA. The results pointed to the following conclusions: (1) VA-RNA is synthesized in the cells throughout the entire period after infections, starting before the onset of viral DNA synthesis. (2) VA-RNA does not participate in protein synthesis as a messenger RNA or a precursor of transfer RNA. (3) The nucleotide sequence homologous to VA-RNA exists as a part of certain species of nuclear high molecular wt RNA in the infected cells.

2578 UPTAKE AND FATE OF THE DNA OF ADENOVIRUS TYPE 2 IN KB CELLS. (Eng.) Groneberg, J. (Inst. Genet., Univ. Cologne, West Germany); Brown, D. T.; Doerfler, W. *Virology* 64(1):115-131; 1975.

The kinetics of uptake and the intracellular fate of human adenovirus DNA were examined in monolayer cultures of KB cells exposed to ^{3}H-labeled adenovirus type 2 DNA. Several procedures were carried out: cell fractionation techniques; acid phosphatase assay; intracellular nucleic extractions; zone sedimentation in neutral and alkaline density gradients; and DNA-DNA hybridization. Cell preparations were variously labeled with [^{14}C]sodium formate or [^{3}H]thymidine and radioactivity was measured by scintillation spectrometry. Infected cells were also examined by electron microscope autoradiography. Studies were carried out in serum-free Eagle's medium under conditions that allowed DNA synthesis to only 18.8% of the level measured in the presence of 10% calf serum. After an initial lag, uptake was linear and reached a plateau at approximately two hours after inoculation, when about 3-9% of the viral DNA were adsorbed. After 2-6 hr, part of the DNA initially adsorbed was shed into the adsorption medium and later partly readsorbed. Viral DNA reached the nucleus beginning at 0.5-2 hr after infection; at 24 hr, 70% of the DNA taken up reached the nucleus. After 24 hr, the amount of label associated with cells exceeded that at any earlier time period. The results were similar when intact type 2 virions were adsorbed to KB cells. Viral DNA was not detected in lysosomes or in cytoplasmic vesicles. Adenovirus-2 DNA was not infectious on HeLa and human embryo kidney cells. Treatment of DNA with pancreatic DNase abolished the activity, and pretreatment with pronase markedly reduced the infectivity. Incubation of type 2 virus DNA with pronase did not alter the sedimentation profiles of viral DNA in neutral and alkaline sucrose gradients. Endonucleolytic fragmentation of viral DNA occurred in the medium. It is suggested that the parental DNA associated with cellular DNA is integrated into the host genome.

2579 A STUDY OF THE ONCOGENICITY OF ADENOVIRUS TYPE 2 TRANSFORMED RAT EMBRYO CELLS. (Eng.) Harwood, L. M. J. (Medical Sch., Univ. of Birmingham, Birmingham B15 2TJ, England); Gallimore, P. H. *Int. J. Cancer* 16(3):498-508; 1975.

The oncogenicity of several adenovirus type 2 (AD-2)-transformed rat cell lines and of several tumor cell lines derived from the transformed cells was studied. Secondary cultures of whole rat embryo fibroblasts (REF), rat embryo muscle (REM), and rat embryo brain (REB) cells from 18-day embryos were transformed with Ad-2. Newborn Hooded Lister (HL) rats and specific pathogen-free Wistar White rats were inoculated ip or sc with 2 x 10^6 to 3 x 10^6 transformed cells from *in vitro* passages 5-15. In some cases, five daily doses of antithymocyte serum (ATS) (0.2 ml) were administered beginning eight days after virus inoculation. Tumors were transplanted by ip or sc inoculation into newborn 18-day-old rats; no immunosuppression was used. All transformed lines and cultured tumor lines were examined for Ad-2 T-antigen by indirect immunofluorescence. The amount of T-antigen and its position within the cell varied considerably between different cell lines, although there was some similarity between the T-antigen staining of a transformed line and the tumors derived from it. Of 48 AD-2-transformed cell lines, only 14 were oncogenic in newborn rats immunosuppressed with ATS, and only one line was oncogenic in nonimmunosuppressed rats. The invasiveness of the tumors resulting from the inoculation of Ad-2-transformed cells appeared to depend to some extent on the route of administration and the transforming virus dose. All tumors resulting from the ip inoculation of lines transformed at 50 and 20 plaque forming units (PFU)/cell invaded and metastasized, while less than 50% of the tumors resulting from the ip inoculation of lines transformed at 10 PFU/cell were invasive; ip inoculation produced more invasive

tumors than sc inoculation. All tumors were histologically identified as undifferentiated round- or spindle-cell sarcomas. The number of multinucleate cells and the proportion of round and spindle cells varied between tumors arising from different transformed lines. Cell lines transformed by adenovirus type 12 were more oncogenic than those transformed by Ad-2. The transforming virus dose had no significant effect on the transplantability of tumors derived from the transformed cells, although the tumor incidence resulting from transplantation was reduced in older rats. The tumor cell lines were not homogeneous in terms of oncogenicity. The results indicate that the most important factor influencing the oncogenicity of Ad-2-transformed cells is the viral dose used for transformation.

2580 COMPLEMENTATION OF HUMAN ADENOVIRUS TYPE 5 *ts* MUTANTS BY HUMAN ADENOVIRUS TYPE 12. (Eng.) Williams, J. (Inst. Virol., Glasgow, Scotland); Young, H.; Austin, P. *J. Virol.* 15(3):675-678; 1975.

To assess the degree to which human adenovirus A and C are functionally related, complementation tests were carried out between type 5 (group A) temperature-sensitive (ts) mutants of 15 different complementation groups and wild type adenovirus type 12 strain 1131. Confluent HeLa cell monolayers were infected either singly at an input multiplicity of 10 plaque-forming U/cell, or doubly with mutant or wild type 12, each at an input multiplicity of 5 plaque-forming U/cell. In a yield from mixed-infected cells, only type 5 will form plaques and only at 32.5 C, unless recombination has taken place. Type 5 mutants included eight enhanced by type 12; hexon-deficient mutants (ts 17 and ts 20); mutants with abnormal hexon transport (ts 1, 2, 3, and 4); and late mutants whose defects are not known (ts 18 and ts 24). In crosses with these mutants, type 12 products functioned effectively to replace defective type 5 functions and enhanced the yield of infectious virus. The other seven mutants that complemented poorly or not at all by type 12 included: DNA-negative mutants (ts 36 and ts 125); fiber-deficient mutants (ts 5, 9, and 22); and two mutants whose defects are not known (ts 19 and ts 31). In these crosses, type 12 products did not substitute for the defective type 5 functions, and yields of infectious virus were enhanced less than 10-fold. Hamster embryo cells were infected with the non-type 12-complemented type 5 mutants singly or doubly as described, and no mutants were enhanced. Coinfection of HeLa cells with type 12 and type 5 had little or no effect on the replication of the wild type adenovirus 5 in these cells, and similar results were obtained with type 5 replication in hamster cells. Monospecific antisera against types 5 and 12 were neutralized by type 5 antiserum and not by type 12; similar results were obtained with the yield from cells coinfected by wild type adenovirus type 5 and strain 1131. Progeny clones from the antigenically-mixed yields were isolated, and all were serotype 5, plaqueing on HeLa cells only at 32.5 C. No evidence was found for viable wild-type recombinants in any cross.

2581 HEXON PEPTIDES OF TYPE 2,3, AND 5 ADENOVIRUSES AND THEIR RELATIONSHIP TO HEXON STRUCTURE. (Eng.) Stinski, M. F. (Sch. Med. Univ. Pennsylvania, Philadelphia); Ginsberg, H. S. *J. Virol.* 15(4):898-905; 1975.

The chemical analysis of three different adenovirus serotypes belonging either to subgroup I (type 3 adenovirus) or III (type 2 and 5 adenoviruses) was carried out. The prototype strains of these viruses, which had been plaque-purified three times, were used. After infecting monolayers of KB cells, virus was quantitated by plaque or fluorescent focus assay. Peptides of hexons from type 2, 5 and 3 adenoviruses were produced by treatment with cyanogen bromide and separated by isoelectric focusing on polyacrylamide gels containing 8 M urea. Peptides with identical isoelectric points, but from different hexon types, were considered to have structural similarities. Accordingly, approximately two-thirds of the type 2 and 5 hexon peptides were considered similar. The pI was indicative of the net charge of the peptide, which was influenced primarily by its amino acid composition. These data implied that the similar peptides originated from a common segment(s) of the polypeptide chain, and that the peptides with distinct pI values were from the variable segment(s) of the polypeptide. When the CNBr peptides of type 2 and 3 hexons were compared, the inconstancy of the $^{3}H:^{14}C$ ratios of the peptides that electrophoresed suggested that some of these may not be identical. The amount of variability was much greater between 2 and 3 hexons than between the hexons of type 2 and 5. When virion hexons were iodinated by the lactoperoxidase method, one set of peptides with pI values greater than 6.8 was iodinated, and this set contained unique as well as some common peptides. Hexons assembled in virions and those free in solution were iodinated differently. These results suggest that, immunologically, the hexons in viral capsids react differently from unassembled hexons because the polypeptide chains assume different folding configurations in the hexon forms and expose different regions of the protein to antibodies.

2582 THE BINDING OF POLYNUCLEOTIDES TO THE DNA POLYMERASE OF AVIAN MYELOBLASTOSIS VIRUS. (Erickson, R. J. (Mol. Biol. Dept., Miles Lab., Inc., Elkhart, Ind.). *Arch. Biochem. Biophys.* 167(1):238-246; 1975.

The relationship between the structure of synthetic nucleic acids and their ability to interact with avian myeloblastosis virus DNA polymerase was studied. This interaction was studied using an adaptation of the membrane filter binding technique. Isotopically labeled *Bacillus subtilis* DNA was used as a substrate. The presence of detergent deoxynucleoside triphosphate or deoxyribonuclease all greatly diminished the retention of the [^{3}H]DNA on the membrane filter, whereas denaturation of the *B. subtilis* DNA significantly increased filter retention. The binding kinetics of the [^{3}H]DNA to the partially purified enzyme preparation was a function of both nucleic acid and protein concentration. Binding of [^{3}H]DNA to methylated bovine serum albumin was compared to the binding in the

esence of the avian myeloblastosis viral polymerase; e major difference was in the stoichiometry of the o reactions, as illustrated by the sigmoidal versus near response curves. Further results indicate that A polymerase activity is retained on the membrane lters in the absence of the nucleic acid. The re- lts also support the hypothesis that the enzyme nds to the filter in the absence of the template. e inhibition of the avian myeloblastosis virus DNA lymerase by the polynucleotide $(U)_n$ was shown to be rongly dependent upon chain length of the polymer. e size dependence was also reflected in its ability inhibit the binding reaction. The unexpected re- ltant reversed size dependence observed for $(dUfl)_n$ s attributed to the reversible nature of the binding say and to noncompetitive or mixed competitive in- bition kinetics. Initial experiment characterizing e binding reaction, and studies on polynucleotide hibition of binding correlate well with previous udies. The nonpurified enzyme preparations employed quired differentiation of potentially specific bind- g from nonspecific aggregation. The data suggest at avian myeloblastosis virus DNA polymerase contains veral distinct binding sites, and that the inhibitory lynucleotides act by interfering with the binding of cleic acid template to the viral enzyme.

583 ANTIGENIC ANALYSIS OF MAJOR STRUCTURAL PROTEINS OF AVIAN LEUKOVIRUSES. (Eng.) Gupta, . (Albert Einstein Coll. Medicine, Bronx, N.Y. 0461); Johnson, J. C.; August, J. T.* *Arch. Biochem. iophys.* 168(2):652-656; 1975.

he four major structural proteins of avian myelo- lastosis virus (AMV), p27, p19, p15, and p12, were urified from serum of C/A leukemic chickens and heir antigenic determinants were examined by radio- mmunoassay. The specificity of rabbit antisera pre- ared against purified p27, p19, and p15 was tested gainst each of the four ^{125}I-labeled purified pro- eins. Each protein was precipitated only by the omologous antisera, suggesting the absence of anti- enic cross-reactivity. Further studies by compe- ition radioimmunoassay confirmed that each protein as antigenically distinct. No competition was ob- erved with the heterologous proteins (even with a 00- to 200-fold excess of unlabeled competing pro- eins), but there was over 95% competition with the omologous proteins. Concentrations of proteins p27, 19, and p15 were measured in uninfected chicken em- ryo fibroblast cells and in cells transformed by ous sarcoma virus (RSV). Protein levels were low n uninfected cells, while the concentrations in RSV- ransformed cells were 520, 1,400, and 650 ng/mg of otal cell protein for p27, p19, and p15, respective- y. It is concluded that synthesis of AMV proteins 27, p19, and p15 is induced from the infecting viral enome and/or from a latent endogenous genome follow- ng virus infection.

584 INTERSPERSION OF SEQUENCES IN AVIAN MYELOBASTOSIS VIRUS RNA THAT RAPIDLY HYBRIDIZE ITH LEUKEMIC CHICKEN CELL DNA. (Eng.) Drohan, W. . (Univ. California Sch. Med., Los Angeles); Shoyab, .; Wall, R.; Baluda, M. A. *J. Virol.* 15(3):550-555; 975.

Localization of the avian myeloblastosis viral genome of the RNA sequences complementary to rapidly reassociating cellular DNA was attempted. The poly(A) at the 3' terminus of the viral genome was used as a reference to localize such sequences in the viral RNA. Fragmented avian myeloblastosis virus (AMV) RNA was adsorbed to poly(U)sepharose and the eluted poly(A)-containing RNA species were fractionated into different sizes. RNA fragments of specific sizes were hybridized with excess leukemic cell DNA. Approximately 80% of the 35S AMV RNA hybridized to leukemic DNA by a C_0t of 10,000 (M/sec/l) in a biphasic curve. In the initial transition, 38% of the RNA hybridized; in the second, an additional 42% hybridized. The C_0t 1/2 of the chicken 28S RNA monophasic hybridization curve was used to estimate the reiteration frequency of the cellular DNA sequences that hybridized to AMV RNA. The midpoint of the initial transition occurred at a C_0t of 85 M/sec/l, and the second was half-completed at 4,000 M/sec/l. These were thus complementary to cellular DNA sequences reiterated about 100 times per haploid genome, and 2-3 times per haploid genome, respectively. Fragments of AMV RNA used as probes in liquid hybridization experiments were prepared. The 35S, 27S, 15.5S, 12.5S and 8S poly(A)-containing fragments were hybridized to chicken DNA. These hybridizations showed rapidly hybridizing sequences in all size classes of AMV RNA. These data indicate that the RNA sequences that hybridize rapidly with excess of cellular DNA are not restricted to any one region of the AMV 35S RNA. It is suggested that they may be randomly distributed over the entire 35S AMV molecule, with some positioned within 200 nucleotides of the poly(A) tract at the 3' end of the RNA.

2585 INTEGRATION OF AVIAN SARCOMA VIRUS SPECIFIC DNA IN MAMMALIAN CHROMATIN. (Eng.) de la Maza, L. M. (Dept. Lab. Medicine and Pathology, Mayo Memorial Building, Univ. Minnesota, Minneapolis, Minn. 55455); Faras, A.; Varmus, H.; Vogt, P. K.; Yunis, J. J. *Exp. Cell. Res.* 93(2): 484-487; 1975.

Constitutive heterochromatin and euchromatin fractions from normal and avian sarcoma virus (ASV)-transformed cells of *Mus musculus* and *Microtus agretis* were isolated in order to characterize the sites of integration of the viral-specific DNA sequences. The cells used were BALB/c 3T3 cells transformed with the B77 strain of ASV, *M. agrestis* fibroblasts transformed with the Schmidt-Ruppin strain of Rous sarcoma virus (UMMA-RSV-21), and a revertant subclone of UMMA-RSV-21. The number of viral copies per diploid genome was studied by the technique of DNA-DNA hybridization in solution; this involved determining the rate of reassociation of ^{3}H-labeled viral DNA with total DNA or DNA from euchromatin, intermediate chromatin, and heterochromatin fractions. Total DNA and euchromatin DNA increased the rate of reassociation approximately two-fold when the ratio of cellular DNA to ^{3}H-labeled viral DNA was 1.3×10^6. This increase indicated the presence of 1-2 viral copies per diploid mammalian genome. The ASV-specific DNA sequences were

found in the euchromatin fraction in all cases. Constitutive heterochromatin and satellite DNA are apparently not favored sites for integration.

2586 MAMMALIAN TROPISM OF B77(RBI) VIRUS. EXPRESSION OF VIRUS GENOME IN THE HAMSTER SARCOMA CELL CLONES. (Eng.) Svec, J. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Hlubinova, K.; Lizonova, A.; Thurzo, V. *Neoplasma* 22(2):133-145; 1975.

The interaction of the B77 virus and its rat variant, B77(RBI), with newborn Syrian hamster cells was studied *in vivo* and *in vitro*. In contrast to B77, the B77(RBI) continuously and efficiently induced progressively growing tumors in hamsters and transformed hamster embryo cells *in vitro*. Both induced tumors and transformed cell cultures showed production of infectious virus and presence of the avian gs-antigen. Clonal analysis of the established hamster sarcoma cell line RBH_{tc} revealed that despite the quantitative differences in the virus production and gs-antigen content among various clonal populations, full expression of the B77(RBI) virus genome had occurred in each cell of the virus-induced hamster sarcoma. The permissive relationship of the B77(RBI) virus with rat and hamster cells, as well as changed antigenic composition, implies that a genetic change of the virus occurred which is reflected in its increased mammalian tropism and its genetically stable virus-productive interaction with mammalian cells. It is proposed that either the rat cells select for the virus variant, or the variant carries part of the rat cell genome.

2587 ANALYSIS OF ANTIGENIC DETERMINANTS OF STRUCTURAL POLYPEPTIDES OF AVIAN TYPE C TUMOR VIRUSES. (Eng.) Stephenson, J. R. (Animal Physiology and Genetics Inst., Beltsville, Md. 20705); Smith, E. J.; Crittenden, L. B.; Aaronson, S. A. *J. Virol.* 16(1):27-33; 1975.

Competition immunoassays were developed and used in comparing the reactivities of representatives of major type C avian virus subgroups. Purified viral polypeptides were labeled with ^{135}I. A double antibody radioimmunoassay was employed for 27,000 molecular weight polypeptides, while competition immunoassays were developed for the 19,000, 15,000, and 12,000 molecular weight polypeptides of avian myeloblastosis virus (AMV) and for the 19,000 and 12,000 polypeptides of RAV-0, a subgroup E avian tumor virus. Reactivity studies indicated a lack of significant type-specific differences between the 127 polypeptides of five major subgroups, including Prague strain Rous sarcoma virus (RSV) of subgroup A (Pr-RSV-A) and C (Pr-RSV-C); Bryan high-titer RSV of subgroups B, BH-RSV(RAV-1) and BH-RSV(RAV-2); Carr-Zilber RSV of subgroup D; and RAV-0. Agarose gel filtration revealed that all three low molecular weight ^{125}I-labeled polypeptides migrated as single peaks, relative to standards; the molecular weights were 19,000, 15,000, and 12,000. Unlabeled p27 failed to compete in homologous AMV p19, p15, or p12 assays. Testing for immunological type specificity of p19, p15, and p12 revealed no detectable difference between the reactivities of AMV, Pr-RSV-A, BH-RSV(RAV-2), or RAV-0 in each assay. Heterologous competition immunoassays demonstrated that the viruses of each subgroup tested reacted similarly f p19, p15, and p12. Homologous immunoassays support the conclusion that type-C specific determinants detected with the prototype viruses were representa tive of their respective subgroups. Thus, p27 is found to be the most group specific, while the lowe molecular weight polypeptides demonstrate type-specific determinants. It is also suggested that subgroups C and D may have evolved differently from subgroups A, B, and E.

2588 SIZE OF VIRUS-SPECIFIC RNA IN B-34, A HA STER TUMOR CELL PRODUCING NUCLEIC ACIDS TYPE C VIRUSES FROM THREE SPECIES. (Eng.) Tsuchid N. (Flow Labs., Inc., Rockville, Md. 20852); Gilde R. V.; Hatanaka, M. *J. Virol.* 16(4):832-837; 1975.

The size distribution of nucleic acid sequences related to hamster, mouse, and rat viruses in B-34 cells was determined by hybridization with cDNA of strict virus specificity. The sedimentation characteristics of the intracellular virus-specific RNA were determined in sucrose gradients after treatmen with dimethylsulfoxide by molecular hybridization using complementary DNA of strict virus specificity. Hamster virus-specific RNA sedimented at 35S (major peak) as is characteristic of productive infection by type C leukemia viruses of other species. Rat virus-specific RNA sedimented at 30S which is charac teristic of the sarcoma virus-related genome found in nonproducer cells transformed by Kirsten sarcoma virus. Both Harvey and Kirsten sarcoma viruses contain a related but not necessarily identical 30S rat specific component which is also found in normal cul tured rat cells. Mouse cells producing Harvey sarcoma virus also contain a rat-specific 30S RNA. Mouse virus-derived sequences also sedimented at 30S in B-34 cells and in a similar size range in Harvey virus-infected mouse cells. The possibility that th mouse and rat-derived sequences are present on a single 30S RNA species which would then be related t sarcomagenic potential is one hypothesis suggested.

2589 INTERSPECIES ANTIGENIC DETERMINANTS OF THE REVERSE TRANSCRIPTASES AND p30 PROTEINS OF MAMMALIAN TYPE C VIRUSES. (Eng.) Sherr, C. J. (Natl. Cancer Inst., Bethesda, Md.); Fedele, L. A.; Benveniste, R. E.; Todaro, G. J. *J. Virol.* 15(6): 1440-1448; 1975.

The interspecies antigenic determinants of the major structural proteins (p30) and reverse transcriptases of type C viruses isolated from several mammalian species (mouse, rat, domestic cat, pig, baboon, woolly monkey, and gibbon) were studied by radioimmunoprecipitation and competitive radioimmunoassays. Three antigenically distinguishable sets of interspecies determinants were demonstrated by both methods. One set of determinants shared by viruses of rodent origin (mouse and rat) could be detected readily in feline leukemia viruses but not in other type C viral groups. The p30 proteins of

urine viruses also contained a second discrete set f antigenic determinants related to those in infecious primate viruses and endogenous porcine viruses, ut not detected in the feline leukemia virus group. he p30 proteins of endogenous viruses of baboons nd domestic cats shared a third set of cross-reacive determinants not detected in type C viruses solated from other species of animals. Enzyme inibition studies performed with antisera raised toard the reverse transcriptases of these same groups f type C viruses showed the same patterns of immuological cross-reactions as observed with p30 proeins. The results suggest that animals of one speies may be infected by type C viruses derived from second, distantly related group of animals, leadng to the incorporation of new virogenes and the ventual perpetuation of these genes in the germ ine.

590 BIOLOGIC AND IMMUNOLOGIC PROPERTIES OF PORCINE TYPE C VIRUSES. (Eng.) Lieber, . M. (Viral Leukemia and Lymphoma Branch, Natl. ancer Inst., Bethesda, Md. 20014); Sher--, C. J.; enveniste, R. E.; Todaro, G. J. *Virology* 66(2): 16-619; 1975.

ix type C virus-producing porcine cell lines [MPK, T-Mo, PORC, PK(15), 38A-1, and PFT] were compared n immunologic and infectivity studies. Reverse ranscriptase inhibition studies were performed sing immune IgG directed against the partially urified polymerase from the PK(15) virus, and aditional experiments were performed to determine if he porcine type C viruses could rescue the Kirsten urine sarcoma virus (Ki-MSV) from mink, rat, and ouse nonproducer cell lines after cocultivation. ttempts were also made to transmit the six porcine ype C viruses to other mammalian host cell lines. ll six porcine cell lines spontaneously began to elease type C viruses after long-term propagation *n vitro*. The reverse transcriptases of all viral solates were inhibited by immune IgG directed gainst the PK(15) polymerase, whereas the enzymes rom feline leukemia virus, the endogenous baboon irus M7, and the endogenous feline virus RD-114 ere not significantly inhibited. Transmission of nfection to other host cell lines was detected nly with MPK and 38A-1, and then only in the porine ST-Iowa host cell line. 38A-1 virus also resued focus-forming Ki-MSV in low titer when coculivated with the mink and rat nonproducer cells, hile the MPK rescued the Ki-MSV genome from the rat onproducer cells and the PORC rescued Ki-MSV from he mouse nonproducer cell line. The other three orcine viruses were unable to rescue the Ki-MSV enome and produce foci of transformation on any ndicator host cell line tested. Since endogenous orcine type C viruses are present as virogens in ll pig cells, and since certain of these viruses an replicate in pig cells, these viruses may play n important role in porcine pathophysiology.

591 STUDIES OF EPSTEIN-BARR VIRUS (EBV)-ASSOCIATED NUCLEAR ANTIGEN. I. ASSAY IN HUMAN YMPHOBLASTOID CELL LINES BY DIRECT AND INDIRECT DETERMINATION OF ^{125}I-IgG BINDING. (Eng.) Brown, T. D. K. (Karolinska Inst., Stockholm, Sweden); Ernberg, I.; Klein, G. *Int. J. Cancer* 15(4):606-616; 1975.

A quantitative assay for Epstein-Barr virus (EBV)-associated nuclear antigen (EBNA) in human lymphoblastoid cells was developed. Cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum and antibiotics. Nuclei were isolated by harvesting and washing cells in 0.01 M N-2-hydroxyethylpiperazine-N'-2-ethane sulfonic acid and agitated with 22.5% Ficoll and 0.1 mM dithiothreitol, and then centrifuged at 1,000 x *g* for 15 min at 4C. Isolated IgG antigen was labeled with ^{125}I by a modified chloramine T method. The assay used employs EBV-associated nuclear antigen-positive or -negative [^{125}I]IgG preparations, and can be used in a direct or indirect manner. [^{125}I]IgG binding is measured by incubation in antigen-containing medium for 18 hr at 4C, and the cells are filtered in 24 mm glass fiber filters and washed in buffer. Indirect assay is performed by a similar incubation, followed by pelleting at 3,500 x *g* for 10 min; the supernatant is then tested for residual binding to target cells or nuclei using the filter. The assay is sensitive, and detected antigen in 10^6 cells. The indirect assay offers a rudimentary test of antigenic relationships among nonproducer cell lines; however, it is a more vigorous test of specificity than the direct assay, once the basic specificity of the binding to the reference cell line has been established. Both antigens of purified nuclear and frozen-thawed cells were efficient in removing [^{125}I]IgG binding against the alternative antigen. Most of the cell lines tested contained the EBV genome, and the expressed EBNA contained an antigen and cross-reacted with Raji cells. Fixatives had an adverse effect on antigen activity. The measurement of blocking of EBV-specific [^{125}I]IgG binding by human sera has demonstrated the potential of this method for the detection of anti-EBNA antibodies.

2592 EPSTEIN-BARR VIRUS-INDUCED TRANSFORMATION OF HUMAN LEUKOCYTES AFTER CELL FRACTIONATION. (Eng.) Schneider, U. (Institut für Klinische Virologie der Universität Erlangen-Nürnberg, 852 Erlangen, Loschgestr. 7, West Germany); zur Hausen, H. *Int. J. Cancer* 15(1):59-66; 1975.

The efficiency of transformation of human lymphocytes after infection with Epstein-Barr virus (EBV) was determined in fractionated and non-fractionated preparations derived from 16 human cord blood samples and two blood samples from adult donors. Macrophage-depleted leukocytes had a consistently lower transformation efficiency than non-fractionated leukocytes. Additional depletion of B-cells resulted in a further decrease. Reduction of T-cells did not significantly change the transformation rate. In nonfractionated leukocyte cultures, as well as in macrophage-depleted and B-cell enriched cultures, colonies of transformed cells were regularly observed within the first week of cultivation. All cell lines established after EBV-infection revealed membrane-bound immunoglobulin. Reconstitution of macrophage-depleted, B-cell enriched or B-cell depleted cultures with autologous macrophages or additions of hetero-

logous human embryonic lung fibroblasts increased the transformation efficiency up to the values of nonfractionated leukocyte preparations. The results support the interpretation that EBV transforms only bone-marrow derived cells of the hematopoietic system. The transformation efficiency is increased by cocultivation of lymphocytes with macrophages and heterologous human fibroblasts which seem to exert a feeder-layer effect by enhancing survival of lymphocytes *in vitro*.

2593 ANTIBODIES TO EPSTEIN-BARR VIRUS-ASSOCIATED NUCLEAR ANTIGEN AND TO OTHER VIRAL AND NON-VIRAL ANTIGENS IN HODGKINS DISEASE. (Eng.) Rocchi, G. (Clinica Medica Generale, III Cattedra, Univ. Rome, Rome, Italy); Tosato, G.; Papa, G.; Ragona, G. *Int. J. Cancer* 16(2):323-328; 1975.

Antibody reactivity to Epstein-Barr virus (EBV)-associated nuclear antigen (EBNA) was investigated with the anticomplement immunofluorescence technique on sera from 100 patients with Hodgkin's disease (HD) and from appropriate controls. Antibody levels to other EBV-determined antigens [i.e., viral capsid (VCA) and early antigens (EA)], to measles and rubella viruses, to cytomegalovirus (CMV), and to *Toxoplasma gondii* were also measured. Results of anti-EBV antibody titrations demonstrated that anti-VCA, anti-EA, and anti-EBNA reactivity was significantly higher in HD patients than in healthy subjects. There was no significant difference between the distribution of high rubella and measles antibody titers in HD and control sera. The geometric mean antibody titer and the incidence of high titer anti-CMV and *T. gondii* antibodies were greater in HD patients than in controls. Analysis of the data according to histological subtypes showed that the condition of lymphocyte depletion in HD patients was associated with the highest anti-EBNA antibody levels and the lymphocyte predominance with the lowest. This pattern seemed to be peculiar for anti-EBV reactivity, since anti-CMV and anti-*T. gondii* antibody levels in the lymphocyte-depleted group of patients did not significantly differ from those of controls. No correlation was found between anti-VCA and anti-EBNA in individual sera of HD patients. This observation suggests that different mechanisms are probably responsible in HD for the release of EBV-related antigens from infected cells.

2594 VIRAL AND CELLULAR DNA SYNTHESIS IN NUCLEI FROM HUMAN LYMPHOCYTES TRANSFORMED BY EPSTEIN-BARR VIRUS. (Eng.) Benz, W. C. (Biological Lab., Harvard Univ., Cambridge, Mass. 02138); Strominger, J. L. *Proc. Natl. Acad. Sci. USA* 72(6):2413-2417; 1975.

A DNA-synthesizing system *in vitro* was developed using nuclei prepared by treatment of human lymphocytes with the detergent Brij 58. Lymphocytes from freshly drawn blood are prepared by Ficoll-hypaque density gradient centrifugation and washed in dextrose/gelatin/veronal buffer. Cultured logarithmic-phase, phytohemagglutinin-stimulated lmphocytes and fresh peripheral lymphocytes are sedimented out of the culture medium, washed, and then resuspended at pH 8.0 The cells are then chilled and diluted with an equal volume of a chilled solution of 0.15 M sucrose, 5 mM $CaCl_2$, 25 mM Hepes (pH 8.0) and 0.5% Brij 58. The suspension is gently agitated on ice for 5 min, diluted 20- to 30-fold with chilled 0.25 M sucrose buffer containing 2% Dextran type C 100, pelleted, and resuspended to a final concentration of 2×10^7 cells/ml. The resultant nuclei were used immediately for determining DNA synthesis using an incorporation mixture containing dATP, dGTP, dCTP, and [^{3}H]dTTP. Radioactivity was determined by trichloracetic acid precipitation. Nuclei from cultured lymphocytes synthesized DNA for as long as five hours (cells in early logarithmic phase); nuclei prepared from cells in midlogarithmic phase continued incorporation for at least 3.5 hr. In nuclei from a parially synchronized line of cultured lymphocytes carrying several hundred copies of the Epstein-Barr viral genome, synthesis *in vitro* was predominantly viral in the early S phase and cellular in late S phase. The synthesis was strongly ATP-dependent, suggesting that the *in vitro* system incorporates radioactivity primarily by a replicative process. This is substantiated by the fact that repair synthesis stimulated by addition of DNase was ATP-independent.

2595 THE SYNTHESIS OF POLYADENYLATED MESSENGER RNA IN HERPES SIMPLEX TYPE I VIRUS INFECTED BHK CELLS. (Eng.) Harris, T. J. R. (Animal Virus Res. Inst., Pirbright, Woking, Surrey, U.K.); Wildy, P. *J. Gen. Virol.* 28(3):299-312; 1975.

The pattern of polyadenylated messenger RNA (mRNA) synthesis in baby hamster kidney cell monolayers, infected under defined conditions with herpes simplex type I virus (40 plaque-forming U/cell) was investigated by polyacrylamide gel electrophoresis of pulse-labeled RNA isolated by oligo dT-cellulose chromatography. Two classes of mRNA molecules were synthesized in infected cells; these were not detected in uninfected cells. The rate of synthesis of the larger, 18 to 30S, RNA class reached a maximum soon after infection and then declined, whereas the rate of synthesis of the 7 to 11S RNA class did not reach a maximum until much later and did not decline. In the presence of cytosine arabinoside (50 μg/ml), the rate of mRNA synthesis in infected cells was reduced but the electrophoretic pattern remained the same. The latter observation is consistent with the view that there are no classical "early" and "late" controls on transcription but rather purely time-dependent controls.

2596 PRESENCE OF HERPES SIMPLEX VIRUS-RELATED ANTIGENS IN TRANSFORMED L CELLS. (Eng.) Chadha, K. C. (Dep. Med. Viral Oncol., Roswell Park Mem. Inst., Buffalo, N. Y.); Munyon, W. *J. Virol.* 15(6):1475-1486; 1975.

Antiserum prepared against herpes simplex virus type 1 (HSV-1)-infected L cells, i.e., lytic antiserum, was shown by an indirect immunofluorescence test to stain 90 to 95% of HSV-transformed L or HeLa cells. Immunofluorescence in these cells was always most

ntense in the perinuclear cytoplasmic region. Sim-
lar results were obtained with antiserum prepared
gainst HSV-transformed L cells. These data indi-
ate that HSV-transformed cells (both L and HeLa)
xpress HSV-related antigens. Antiserum prepared
gainst HSV-1-transformed L cells was found to ag-
lutinate purified HSV type 1 virions but failed
o neutralize infectivity, suggesting that HSV-1
tructural antigens are expressed in HSV-1-trans-
ormed L cells. Immunodiffusion studies showed that
t least two HSV-related antigens could be demonstra-
ed with antigens from HSV-1-transformed L cells
nd transformed cell antiserum. These two antigens
ere shown to be present in all clonal lines of
SV-1-transformed cells examined, six L cell lines
nd one HeLa cell line. Therefore, transformation
f cells by HSV-1 must be associated with the pre-
ence of these two antigens. Experiments showed
hat there are species of HSV-related antibody in
SV-transformed cell antiserum that could not be
bsorbed out with antigens from HSV-infected L cells.
ntibodies present in lytic antiserum were completely
emoved by antigen preparations from cells lytically
nfected with HSV-1. Also, lytic antiserum failed
o block HSV-related staining of transformed L cells
n a direct immunofluorescence test.

597 DETECTION OF A VIRUS-SPECIFIC ANTIGEN ON THE SURFACE OF HERPES SIMPLEX VIRUS-RANSFORMED CELLS. (Eng.) Reed, C. L. (Milton S. ershey Med. Cent., Pennsylvania State Univ., Her-hey); Cohen, G. H.; Rapp, F. *J. Virol.* 15(3):668-70; 1975.

erpes simplex virus type 1 (HSV-1) and type 2 (HSV-)-transformed hamster embryo cells were tested for he presence of surface virus-specific antigens. The iruses had been inactivated either by UV irradiation r by neutral red dye and visible light. Antiserum repared against the virus-specific antigenic frac-ion (CP-1) did not react with uninfected controls. ll three cell lines transformed by UV-irradiated SV-1 and none of five cell lines transformed by HSV- reacted positively to anti-CP-1 serum. The mean ositive reactivity was about 50%, and similar results ere obtained with cells at passages 22 and 96 and at ntervals through passage 140. The 14-012-8-1 T#10 ine was derived from the 14-012-8-1 line by inocula-ion into syngeneic hamsters. The subsequent tumors ere removed and reinoculated. Expression of CP-1 ntigen was retained after four *in vivo* passages. ell lines transformed by neutral red dye and visible ight-inactivated HSV-1 and HSV-2 did not react with nti-CP-1 serum. Hamster cells transformed by UV-nactivated cytomegalovirus and by PARA-adenovirus 7 lso did not react. These experiments indicate that virus-specific antigen occurs on the surface mem-ranes of cells transformed by the herpes simplex irus type 1.

598 ONCOGENIC TRANSFORMATION OF PRIMARY HAMSTER CELLS BY HERPES SIMPLEX VIRUS TYPE 2 (HSV-2) AND AN HSV-2 TEMPERATURE-SENSITIVE MUTANT. (Eng.) Kimura, S. (Baylor Coll. Med., Houston, Tex.); lannery, V. L.; Levy, B.; Schaffer, P. A. *Int. J. Cancer* 15(5):786-798; 1975.

The induction, isolation, and preliminary characterization of six cell lines transformed by UV-irradiated herpes simplex virus type 2 (HSV-2) and a temperature sensitive mutant (ts mutant) of HSV-2 are described. Irradiated virus was adsorbed to 2-day-old hamster embryo fibroblasts for two hours at a multiplicity of 400 UV-inactivated particles per cell. Rabbit antiserum to HSV-2 was added to half the infected cultures before incubation. Foci of transformed cells were picked 40 days after infection and grown to confluency. In additional experiments, hamster embryo fibroblast monolayers were pretreated with 5-bromodeoxyuridine or UV irradiation prior to infection and cell foci were picked 34 days after infection. To obtain transformation with ts mutants of HSV, hamster embryo fibroblast monolayers were infected at a multiplicity of 5-10 plaque forming units per cell, and the virus was adsorbed for two hours at 37 C. Infected monolayers were incubated at the nonpermissive temperature, and cell foci were picked 30 days after infection. Cultures were tested for oncogenicity by injecting 0.1 ml (5×10^5 cells) of each cell suspension sc into newborn hamsters which were observed for six months for tumor development. Two of 25 foci picked 40 days after infection could be subcultured indefinitely. Three cell lines were established from foci picked from pretreated infected cultures: two from 18 foci derived from UV-treated cultures, and one from 29 foci picked from bromodeoxyuridine-pretreated cultures. One of eight foci picked from cultures infected with a HSV-2 DNA^- ts mutant survived more than 70 passages. Two additional mutant-transformed cell lines were established from 130 foci picked from cultures infected with a DNA^+ HSV-1 ts mutant and a DNA^+ HSV-2 ts mutant. All six transformed cell lines produced undifferentiated fibrosarcomas in newborn hamsters after, but not before, 33 passages. Four of six lines produced metastatic tumors in the lungs. Sera from tumor-bearing hamsters contained neutralizing antibody to HSV-2. HSV-specific cell-surface antigen was detected by immunofluorescence in all six of the lines established from primary tumors. Antibody to an early, HSV-specific, nonstructural polypeptide reacted by immunofluorescence with antigen(s) in fixed preparations of 3 of 6 tumor cell lines. No type-C virus group-specific-3 antigen was detected in either transformed or tumor-cell lines. It is suggested that the absence of such markers is presumptive evidence that type-C virus played no role in the transforming event, and that transformation was induced by HSV-2.

2599 EXPERIMENTAL INFECTION WITH HERPES SIMPLEX VIRUS TYPE 2 IN NEWBORN RATS: EFFECTS OF TREATMENT WITH IODODEOXYURIDINE AND CYTOSINE ARABINOSIDE. (Eng.) Percy, D. H. (Health Sciences Centre, Univ. Western Ontario, London 72, Ontario, Canada); Hatch, L. A. *J. Infect. Dis.* 132(3):256-261; 1975.

Sprague-Dawley rats were inoculated ip, within 36 hr of birth, with 0.05 ml of either of two strains of herpes simplex virus type 2. The effects of treatment for five days with either 5 iododeoxyuridine or cytosine arabinoside (12.5 or 25 mg/kg/day) were

studied. Evaluation of treatment based on rate of survival, incidence of lesions, and isolation of virus from the CNS (100 or 200 mg/kg/day) showed no appreciable difference between treated and untreated littermates. Drug-related effects of retardation of growth and defective development of the cerebellum and retina were found. Areas of retinal hyperplasia were present in the majority of rats that survived for more than ten days after treatment with the higher 5-iododeoxyuridine dose. Cerebellar hypoplasia and marked retinal dysplasia were present in animals treated with either dose of cytosine arabinoside, particularly those killed at 14 days. The virus content of brain and skin suggested that neither drug had been effective. The validity of therapy with either of these drugs in generalized herpetic infections is questioned because activity was minimal against the infecting agent even when the dosage of the drug was sufficient to produce serious defects in certain developing tissues.

2600 HERPESVIRUS ANTIBODIES AND ANTIGENS IN PATIENTS WITH CERVICAL ANAPLASIA AND IN CONTROLS. (Eng.) Pacsa, A. S. (University Medical Sch., H-7643 Pecs, Hungary); Kummerlander, L.; Pejtsik, B.; Pali, K. *J. Natl. Cancer Inst.* 55(4):775-781; 1975.

Antibody activity to herpesvirus hominis type 2 (HVH-2) in 151 women cured of cervical carcinoma (60 *in situ*, 91 invasive) and in 106 controls was investigated. The two control groups consisted of women with or without cervical atypia; controls of both groups were matched to women with cervical atypia by age (10-yr intervals), social status, marital status, number of pregnancies, and number of children. The antibody activity to HVH-2 differed significantly, especially between the *in situ* (73%) and control (17%) groups. Sera of 57 patients with cervical atypia showed an increased antibody to HVH-2 (58%), compared with that of the 57 matched controls (23%). Antibodies to cytomegalovirus (CMV) were detected more frequently in sera of women with atypia (61%) than in sera of women with cervical disorders other than atypia (42%) or in sera of healthy controls (33%). HVH antigens were present in cervical cells from patients with atypia and from matched controls. Not only exfoliated (imprints) but also cultured and cocultured cervical cells contained HVH antigens; there was no correlation bewteen antigen positivity and antibody activity to HVH-2. The data support the association between HVH-2 and cervical anaplasia and indicate that CMV may also be implicated in its etiology.

2601 SEGREGATION OF RD-114 FeLV-RELATED SEQUENCES IN CROSSES BETWEEN DOMESTIC CAT AND LEOPARD CAT. (Eng.) Benveniste, R. E. (Natl. Cancer Inst., Bethesda, Md. 20014); Todaro, G. J. *Nature* 257(5527):506-508; 1975.

Male leopard cats (*Felis bengalensis*) lacking RD-114 and feline leukemia virus (FeLV)-related DNA sequences (RD^-, FL^-) were mated to domestic cats (*F. catus*, RD^+, FL^+). The segregation of both sets of virogenes was studied in F_1 hybrids and in the progeny of a backcross to the RD^-, FL^- parent. The cellular DNA of the F_1 hybrids contained half the number of each set of sequences present in the domestic cat parent. One of two kittens obtained from an F_1 hybrid female backcrossed to the leopard cat contained all the RD-114-related information but, like the F_1 parent, only half the number of virogene copies. This kitten also had the same number of FeLV-related virogene copies of F_1 parent. The second kitten lacked both RD-114 and FeLV-related DNA sequences. In the backcrossed animals, the RD and FL virogenes segregated together in a manner consistent with their localization at a single chromosomal site. The data rule out both the possibility that each of the multiple copies of RD-114 or FeLV-related virogenes occurs on a different linkage group, and models of nonchromosomal inheritance of the multiple viral copies.

2602 FRIEND LEUKEMIA AND ENDOGENOUS VIRUSES. I. PRODUCTION OF FRIEND AND ENDOGENOUS C-TYPE PARTICLES BY MOUSE CELLS CULTURED *IN VITRO*. (Eng.) Stewart, M. L. (Albert Einstein Coll. Med., Bronx, N.Y.); Maizel, J. V., Jr. *Virology* 65(1):55-66; 1975.

The production of Friend leukemia virus (FLV) and other particles produced by BALB/c mouse cells was followed in serial cultures after infection *in vitro*. BALB/c mouse cells, free of C-type particles as shown by electron microscopy, were seeded at $5 \times 10^5/75\ cm^2$ and infected with 4 ml of mouse spleen extract containing 2×10^6 plaque forming units FLV. Cells were maintained in exponential phase of growth by transfer at 90% confluency. RNA in cells was radiolabeled with [^{3}H]uridine (50 μCi/ml added to the medium for 16 hr. After removal of cells from the medium by centrifugation, the supernatant medium was centrifuged to remove subcellular debris before the addition of concanavalin A for 2.5 hr. Concanavalin A-agglutinated virus was fractioned in sucrose equilibrium gradients. Virus production was assayed by analysis of 60-70S RNA in sodium dodecyl sulfate-solubilized Concanavalin A aggregates. Newly infected cells released infectious leukemia virus (density 1.16) together with a heterogeneous population of other particles of densities 1.18, 1.22, and 1.24. A temporal relationship existed between the kinds of particles produced by the cells and the extent of cell passage after infection. Particles of a density greater than 1.16 were released in gradually diminishing amounts during successive cell passages. Virus was continually released by the cells during these serial passages, and it was consistently and quantitatively isolated by agglutination. Three days after infection, 65S RNA was detectable in particles released into the culture medium. The amount of 65S RNA increased significantly through the second cell passage and remained constant in subsequent passages. Infected and uninfected eighth passage cells were examined in thin sections in the electron microscope for C-type particles. Extracellular virus particles 100-150 nm in diameter having typical C-type morphology were visible in sections from both cultures. These

articles were morphologically indistinguishable rom FLV. They bound ferritin-conjugated concanava- in A and contained 60-70S RNA, but they had differ- nt buoyant densities. It is concluded that endo- enous virus produced by FLV-infected cells is simi- ar but not identical to endogenous virus produced y uninfected cells.

503 FRIEND LEUKEMIA AND MOUSE ENDOGENOUS VIRUSES. II. PROTEINS OF FRIEND LEUKEMIA ND MOUSE ENDOGENOUS C-TYPE PARTICLES PRODUCED BY ALB/c MOUSE CELL CULTURES. (Eng.) Stewart, M. L. Albert Einstein Coll. Med., Bronx, N.Y.); Maizel, . V., Jr. *Virology* 65(1):67-76; 1975.

he polypeptide patterns of concanavalin A (con A)- solated Friend leukemia virus (FLV) and other par- icles of density 1.18 that are spontaneously pro- uced by Friend-infected and uninfected BALB/c mouse ells were analyzed in high-resolution sodium dodecyl ulfate-acrylamide gradient gels. The virus particles ere labeled with ^{35}S-methionine. Agglutination of irions by con A and fractionation of α-methyl man- ose-dissociated complexes in sucrose equilibrium radients yielded a pattern associated with FLV (den- ity 1.16) containing at least 20 polypeptides of olecular wt 30,000-218,000. The pattern included he major structural polypeptide of murine leukemia irus, molecular wt 34,000, and, compared to pub- ished patterns, had a lower proportion of smaller olypeptides. Relative to serum albumin, a major omponent of culture medium, virion polypeptides were urified at least 50,000-fold, and the specific leu- emia virus infectivity of isolates was approximately plaque forming unit/800 particles. Though they ere morphologically indistinguishable from FLV, and imilarly contained viral 60-70S RNA, spontaneously rising BALB/c endogenous viruses (density 1.18) pos- essed a recognizable complement of at least 26 poly- eptides including a major one of molecular wt 44,000. he pattern included a glycopolypeptide of molecular t 14,000 not found in FLV. Like the FLV pattern, the ajority of polypeptides were of molecular wt 30,000- 18,000. The greater number of polypeptides in endo- enous virus suggests that the pattern may be derived rom a mixture of particles. The greater amount of 4,000 molecular wt polypeptide in endogenous virus uggests the possibility that some mixing took place ith coproduced FLV.

2604 INHIBITORY EFFECT OF INTERFERON ON MULTIPLICATION OF FRIEND LEUKEMIA CELLS *IN VIVO*. (Eng.) Rossi, G. B. (Sezione di Virologia, Istituto Superiore di Sanita, 00161 Rome, Italy); Marchegiani, M.; Matarese, G. P.; Gresser, I. *J. Natl. Cancer Inst.* 54(4):993-996; 1975.

The effect of daily interferon treatment on the capacity of Friend leukemic cells to colonize the spleen was studied in irradiated (800 R X-rays at 53.5 cm) and nonirradiated DBA/2 mice. Intravenous injections of viral preparations at a titer of 10^8 mean egg infection dose/ml were given to the mice. Irradiated and nonirradiated mice were given iv injections of the desired cell concentration on day 0. Irradiated mice were inoculated ip on day 5 and nonirradiated mice on days 7-9 with 10^{-7} M of 5-fluoro-2'-deoxyuridine to depress endogenous thymidine synthesis; 30-60 min later they were inoculated with 0.2-0.5 μCi of ^{125}5-iodo-2'-deoxyuridine (^{125}IUR) to monitor leukemic cell multiplication. The uptake of ^{125}IUR in the spleen increased in inoculated mice with Friend leukemic cells as compared with uninoculated mice. This uptake was inhibited when treated with interferon. The ^{125}IUR uptake in leukemic-infected mice was much greater than those given by frozen and thawed cells representing a difference in the proliferation of injected viable cells. Daily treatment of mice with interferon inhibited this leukemia-induced ^{125}IUR uptake. Treatment of mice with mouse cell culture interferon or with Newcastle disease virus (NDV) inhibited the ^{125}IUR uptake, whereas treatment with either rabbit interferon or control cell cultures had no effect. These results show that daily interferon treatment can inhibit the multiplication of transplanted Friend leukemic cells in the spleen. The influence of interferon may be a direct or indirect (host-mediated) interference of cell multiplication.

2605 ERYTHROID COLONY INDUCTION WITHOUT ERYTHROPOIETIN BY FRIEND LEUKEMIA VIRUS *IN VITRO*. (Eng.) Clarke, B. J. (Faculty of Medicine, Univ. Toronto, Toronto, Ontario, M5S 1A8, Canada); Axelrad*, A. A.; Shreeve, M. M.; McLeod, D. L. *Proc. Natl. Acad. Sci. USA* 72(9):3556-3560; 1975.

The induction of erythroid colony formation without erythropoietin (Epo) by bone marrow cells infected *in vitro* with Friend leukemia virus (FV) is reported. Bone marrow cells from C3Hf/BiUt mice were treated with media from IS cell cultures, which continuously produce FV in culture. The cells were then incubated for two days in plasma culture, and the number of erythroid colonies were observed. The effects of centrifuging the IS medium on the induction of erythroid colonies was determined, as were the effects of subjecting it to elevated temperatures (56 C). In addition, determinations were made of the effect of using bone marrow cells from different mouse strains (SIM and C57BL/6), the fetal calf serum concentration (0-20%), the presence of XC plaque-forming virus in the FV-containing medium, and the dose of FV-containing IS culture medium. Compared with control medium-treated cultures, the number of erythroid colonies was 2- to 3-fold higher in the IS medium-treated cultures. The activity in the IS medium could be removed by centrifugation and recovered from the resuspended pellet in concentrated pellets. The number of erythroid colonies produced *in vitro* was related to the Friend spleen focus-forming virus (SFFV) titer *in vivo*. Similarly, both the capacity of IS culture medium to induce erythroid colonies and its Friend SFFV titer were lost after heating. While Epo induced the formation of erythroid colonies by bone marrow cells independently of their strain of origin, the IS medium induced erythroid colony formation only when mixed with C3H or SIM bone marrow cells, but not with those of the B6 strain. Reduction of the

fetal calf serum concentration lowered the number of erythroid colonies in control cultures, but had much less effect on the IS medium-treated cultures. The presence of Friend SFFV activity was necessary for erythroid colony induction by FV *in vitro*, and the number of erythroid colonies produced in the IS medium-treated cultures was approximately proportional to the concentration of IS medium. Also, the capacity of IS medium to induce the formation of erythroid colonies *in vitro* was related to its capacity to induce spleen foci *in vivo*. This system should prove useful for the *in vitro* investigation of Friend virus-host interactions which lead to Epo-independent erythropoiesis.

2606 ADAPTATION OF N-TROPIC FRIEND LEUKAEMIA VIRUS AND ITS MURINE SARCOMA VIRUS PSEUDOTYPE TO NON-PERMISSIVE B-TYPE C57BL/6 MOUSE CELL LINE. (Eng.) Yoshikura, H. (Inst. Medical Science, Univ. Tokyo, Japan). *J. Gen. Virol.* 29(1):1-9; 1975.

The adaptation of N-tropic Friend leukemia virus (FLV) and a murine sarcoma virus (MuSV) pseudotype to nonpermissive B-type cells was studied. The MuSV pseudotype was obtained by infecting S+L- cells with the FLV. N-tropic FLV was serially passaged in the B-type C57BL/6 mouse cell line, YH-7, as was MuSV(FLV). After a single passage, the infectious efficiency of FLV in the restrictive YH-7 cells was significantly increased. This adapted character of FLV could be reversed by a single passage in permissive N-type MLg cells. The true host range conversion from N to NB was accomplished after 11-12 passages in YH-7 cells; no reversion to N-tropism was observed with the NB-tropic-converted twelfth passage FLV in YH-7 cells. When the NB-tropic Rauscher leukemia virus (RLV) was serially diluted in the medium or in FLV and used to infect the YH-7 cells, the virus in the harvest was predominantly NB-tropic. This was true even if the N-tropic FLV existed in a large excess. The N to NB conversion of FLV was much slower than that of MuSV(FLV); in the latter, the host range conversion from N to NB was accomplished in two passages, the converted virus remaining NB-tropic even after propagation back into the N-type MLg cells. Thus, the N-tropic FLV was readily converted to NB-tropic virus in the presence of the MuSV genome, but the conversion required many more passages in the absence of MuSV.

2607 ECOTROPIC LEUKEMIA VIRUSES IN CONGENIC C57BL MICE: NATURAL DISSEMINATION BY MILK-BORNE INFECTION. (Eng.) Melief, C. J. M. (Tufts Univ. Sch. Medicine, 171 Harrison Ave., Boston, Mass. 02111); Louie, S.; Schwartz, R. S.* *J. Natl. Cancer Inst.* 55(3):691-698; 1975.

The incidence of infectious murine leukemia virus (MuLV) was studied in ten lines of congenic-resistant C57BL mice. No constant relationship between the incidence of MuLV and the H-2 complex was apparent. Two lines, B10 and B10.A, were examined in detail because the incidence of MuLV in B10 was low and the virus appeared relatively late in life, whereas B10.A animals had a relatively high incidence of infection by MuLV early in life. Further studies of B10.A mice revealed an almost universal concordance between the virologic status of the mother and her offspring. This was particularly evident when (B10 x B10.A)F_1 animals were compared with (B10.A x B10)F_1 mice. Although genetically identical, the incidence of MuLV in the latter was high, whereas in the former it was low. Transmission of MuLV by milk was proved by foster-nursing experiments; when the infants of MuLV-positive B10.A mothers were suckled on MuLV-negative B10.A mothers, they were free of MuLV. Milk-borne infection may account for the natural dissemination of MuLV among some inbred lines of mice.

2608 HYBRIDIZATION OF MOUSE LEUKEMIA VIRUS c-DNA TO MOUSE REPEATED DNA SEQUENCES. (Eng.) Ginelli, E. (Centro di Patologia Molecolare, Via Pace 15, I-20122 Milano, Italy); Gianni, A. M.; Corneo, G.; Polli, E. *Acta Haematol. (Basel)* 54(4): 221-226; 1975.

Hybridization experiments between mouse leukemia virus synthetic ^{3}H-DNA probe and mouse main band and satellite DNAs were carried out to determine the percentage of viral sequences in satellite DNA. Transformed mouse cell line 1798 was obtained by infection of a normal 3T6 mouse with Harvey strain Murine sarcoma virus. Mouse satellite DNA was isolated from main band DNA by silver-cesium or cesium chloride centrifugation. Viral DNA probe was hybridized to isolated satellite and main band DNAs at 60 C in 0.48 M phosphate buffer. The amount of radioactive viral complementary DNA hybridized was evaluated by batch elution at 60 C. No higher concentrations of viral sequences were observed in the satellite DNA; the hybridization was not due to highly reiterated sequences present in the viral genome. There was no significant difference between main band and satellite and main band DNAs at 60 C in 0.48 M phosphate buffer. The amount of radioactive viral complementary DNA hybridized was evaluated by batch elution at 60 C. No higher concentrations of viral sequences were observed in the satellite DNA; the hybridization was not due to highly reiterated sequences present in the viral genome. There was no significant difference between main band and satellite DNAs; however, a difference in the thermal stability in the hybrids obtained with normal and transformed DNA was evident. The viral sequences appeared to be enriched in the fast renaturing intermediate main band DNA.

2609 IDENTIFICATION OF THE VIRIONS IN THE *IN VITRO* L1210(V) LEUKEMIA CELL LINES BY MORPHOLOGICAL, VIROLOGICAL, AND IMMUNOLOGICAL TECHNIQUES. (Eng.) Chen, P. L. (Inst. Med. Res., Camden, N.J.); Hutchison, D. J.; Sarkar, N. H.; Kramarsky, B.; Moore, D. H. *Cancer Res.* 35(3):718-728; 1975.

Studies of the structural and biological features of virus in two cell lines, L1210(V) Glu^- and L1210(V)-Asn^-, are reported. Sera used in immunological tests included: normal rabbit, normal rat, rabbit anti-mammary tumor virus of RIII milk, rat anti-Gross leukemia virus, rat anti-Rauscher leukemia virus proteins, goat

anti-rabbit α-globulin, and anti-rat α-globulin. The cultures were subjected to immunoelectron microscopic examinations and immunodiffusion tests. The cell lines from *in vitro* cultures were inoculated ip into four strains of mice: C57Bl, Af, RIIIf, and BALB/c, having mammary tumor incidences of 0, 47, 10, and 27%, respectively. A fifth mouse strain, $BD2F_1$, was used in initial infectivity experiments. The investigation involved thin-section, whole-cell mount, and negative-strain electron microscopy. About 20-30% of the cells of both lines bore two conspicuous surface extensions, i.e., stout protrusions of varying size and shape, and microvilli. Cells cultured *in vitro* gradually lost their efficiency in virion production, and required passage *in vivo* to replenish their productivity. Intracytoplasmic A-particles exhibited three general distribution patterns: aggregated, scattered, and near the cell margin. Five modes of particle morphogenesis were observed: (1) spiked virions with nucleoids in the process of assembly, (2) spiked virions with preformed nucleoids, (3) spikeless particles with nucleoids in the process of assembly, (4) intracisternal A-particles, and (5) spikeless particles with preformed nucleoids. Only two morphologically distinct types of extracellular particles were observed: virions covered by uniformly spaced surface spikes, and virions with spikeless envelopes. Density gradient separation of B- and C-type particles was unsuccessful; the majority of the budding virions of L1210 cells prepared for immuno-electron microscopy had performed nucleoids. Generalized leukemia occurred in 100% of the $BD2F_1$ and 47% of the BALB/c mice within 8-10 days after inoculation. However, generalized leukemia did not occur in any of the C57BL, Af, and RIIIf strains tested; the purified virions were also ineffective. The L1210(V) cell suspension lines, differing in one nutritional requirement, nonetheless produced the same types of viral particles. That the cells also gave cytoplasmic immunofluorescence when tested against the six protein antigens of Rauscher virus and demonstrated the strongest reaction to the 30,000 molecular weight protein, suggests that at least some of the viral antigens are related to Rauscher leukemia virus.

2610 *IN VITRO* INFECTION OF LYMPHOID CELLS BY THYMOTROPIC RADIATION LEUKEMIA VIRUS GROWN *IN VITRO*. (Eng.) Haas, M. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel); Hilgers, J. *Proc. Natl. Acad. Sci. USA* 72(9):3546-3550; 1975.

Some of the biological properties of a cell-culture-derived lymphatic leukemia virus (LLV) of the mouse are described. Murine lymphoid cells were infected *in vitro* with purified leukemogenic radiation leukemia virus (RadLV) produced by virus-induced lymphoblast cell lines (BALB/3T3, NIH/3T3, normal rat kidney, BL-5, M-6, and SC-1). Using indirect immunofluorescence and xc plaque assays, thymocytes were shown to be highly susceptible to infection by the virus, whereas murine or other fibroblasts were refractory to it. Murine bone marrow and spleen cells were shown to be much less sensitive to infection by this thymotropic RadLV. By comparison, a B-tropic RadLV isolate (RadLV*), propagated on a mouse fibroblast cell line, was noninfectious for lymphoid cells but infected fibroblasts. A correlation was shown to exist between *in vitro* infection of thymocytes, as assayed by immunofluorescence, and *in vivo* leukemogenicity of the thymotropic RadLV. This constitutes a rapid *in vitro* test for *in vivo* leukemogenicity of a natural lymphatic leukemia virus.

2611 HEMOLYTIC ANEMIA INDUCED BY MURINE ERYTHROBLASTOSIS VIRUS: POSSIBLE MECHANISMS OF HEMOLYSIS AND EFFECTS OF AN INTERFERON INDUCER. (Eng.) Slamon, D. J. (Dept. Anatomy, Univ. Chicago, 1025 E. 57th St., Chicago, Ill. 60637). *J. Natl. Cancer Inst.* 55(2):329-338; 1975.

Viral, morphologic, and biochemical differences between the murine erythroblastosis virus (MuEV, also called murine leukemia virus-Kirsten)-infected and MuEV-infected, poly I·poly C treated W/Fu rats were studied to gain insight into the nature of the hemolytic anemia seen in erythroblastosis and the possible mechanisms by which poly I·poly C prevents the development of this disorder. The ultrastructure of the virus and of the viral reproductive process were also studied. MuEV infection in 1-2 wk-old rats induced a fulminant hemolytic anemia accompanied by a marked splenomegaly and the characteristic splenic histology seen in MuEV-induced erythroblastosis. Animals treated with poly I·poly C within three days after MuEV infection did not develop splenomegaly or the histologic changes, although those beginning treatment after day 3 post-infection showed a pathologic response pattern similar to that in the untreated animals. In comparison with the untreated rats, animals receiving poly I·poly C also had markedly reduced levels of virus reproduction as measured by bioassay and electron microscopic examination of the erythroid cells. The proliferation of erythroblasts after MuEV infection in the animals not receiving poly I·poly C appeared to be an erythropoietin-dependent compensatory response to hemolysis. The hemolysis itself seemed to require virus reproduction in the affected cell types. Morphologically, the virus itself was indistinguishable from any other C-type RNA viruses in the murine leukemia-sarcoma group. The budding process during virus replication began as a dense linear thickening immediately subjacent to the plasma membrane. As the assembly process continued, the nucleoid grew in size and budded from the cell, taking with it the overlying plasma membrane and underlying cytoplasm. The results suggest that poly I·poly C treatment in MuEV-infected rats inhibits virus reproduction and thus may circumvent the hemolytic disease syndrome.

2612 VIRAL-RELATED INFORMATION IN ONCORNAVIRUS-LIKE PARTICLES ISOLATED FROM CULTURES OF MARROW CELLS FROM LEUKEMIC PATIENTS IN RELAPSE AND REMISSION. (Eng.) Mak, T. W. (Dept. Med. Biophys., Univ. Toronto, Canada); Kurtz, S.; Manaster, J.; Housman, D. *Proc. Natl. Acad. Sci. USA* 72(2):623-627; 1975.

The nucleic acid component of particles found in tissue from patients with leukemia was characterized. Twenty-nine marrow specimens were obtained from 26

patients with leukemia, and nine specimens were obtained from patients without leukemia. The size distribution of RNA contained in particles released by leukemic cells was analyzed by velocity sedimentation in sucrose gradients containing sodium dodecyl sulfate. As a control, a tissue culture cell line actively producing a murine oncornavirus (Friend murine leukemia virus) was incubated under conditions identical to those used for the marrow samples. Seventeen marrow samples obtained from leukemic patients in relapse or in a chronic phase of the disease yielded particles containing high-molecular-weight RNA with a sedimentation velocity (about 70S) similar to that obtained for murine oncornavirus RNA. These particles were released even after a short period (16-18 hr) from cultures of cells from patients with the following leukemias: acute myeloblastic, acute lymphoblastic, acute myelomonocytic, chronic lymphocytic (in relapse or chronic phase), and chronic myelocytic (in chronic phase). Eight of nine marrow samples from nonleukemic patients did not yield detectable high-molecular-weight RNA. Among patients in firm hematological remission, 3 of 3 samples from patients with acute lymphoblastic leukemia and 3 of 9 samples from patients with acute myeloblastic leukemia were positive for high-molecular-weight RNA. The base sequence of the RNA in particles was characterized by synthesizing complementary [^{3}H]DNA in an endogenous reaction and hybridizing to excess RNA from known oncornaviruses. Hybridization of 40-60% of input complementary DNA to simian sarcoma virus RNA was detected. No homology was detected with an avian oncornavirus (Rous sarcoma virus), while an intermediate level of homology (10-30%) was found in hybridization to murine sarcoma virus (Kirsten) and murine leukemia viruses (Raucher, Moloney, and Gross). The results provide additional evidence that the virus-related particles produced by marrow from leukemia patients share many properties with viruses known to be oncogenic in other species.

2613 BIOLOGICAL AND PHYSICAL MODIFICATIONS OF A MURINE ONCORNAVIRUS BY 2-DEOXY-D-GLUCOSE. (Eng.) Prochownik, E. V. (Pritzker Sch. Med., Univ. Chicago, Ill.); Panem, S.; Kirsten, W. H. *J. Virol.* 15(6):1323-1331, 1975.

The effect of 2-deoxy-D-glucose (2-DG) on the release of Kirsten murine sarcoma-leukemia virus [KiMSV-(KiMuLV)] from transformed rat kidney (NRK-K) cells was investigated. ^{3}Uridine-labeled virus was pelleted and banded in sucrose. The total number of ^{3}H counts per minute in the density region of the viral peak ($\sim$1.14-1.18 g/cm^3) was counted. Aliquots (50 µl) of each gradient fraction were assayed for protein. At 30 mM 2-DG, RNA synthesis in NRK-K cells was inhibited by approximately 30%, and protein synthesis was inhibited by as much as 80% of control levels. RNA synthesis was not inhibited in nontransformed normal rat kidney (NRK) cells, although protein synthesis was equally suppressed in NRK and NRK-K cells. After treatment with 2-DG, the release of physical particles of KiMSV(KiMuLV) from NRK-K cells was not reduced as determined by equilibrium density gradient centrifugation and assays for RNA-dependent DNA polymerase of culture fluids. The ability to detect virion-associated radioactivity in equilibrium density gradients was dependent on the conditions of labeling. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of KiMSV(KiMuLV) proteins revealed marked structural alterations after propagation of the virus in 30 mM 2-DG. These alterations may account for the observed loss of transforming ability of KiMSV(KiMuLV). It is concluded that 2-DG inhibits the appearance of transforming particles of the virus and suppresses cellular RNA and protein synthesis, but does not affect the yield of physical viral particles.

2614 DERIVATION OF MOUSE SARCOMA VIRUS (KIRSTEN) BY ACQUISITION OF GENES FROM HETEROLOGOUS HOST. (Eng.) Roy-Burman, P. (Univ. of Southern California Sch. of Medicine, Los Angeles, Calif. 90033); Klement, V. *J. Gen. Virol.* 28(2):193-198; 1975.

The nucleotide sequences of the 70S RNA genome of the Kirsten mouse sarcoma virus (Ki-MSV) were compared with those of mouse erythroblastosis virus (MEV) which had given rise to Ki-MSV after *in vivo* propagation in the rat. The RNA of the Ki-MSV and MEV viruses was labeled with ^{3}H, and the labeled 70S RNA was extracted and hybridized with alkali-treated DNA from various cells and tissues. Virus RNA-cellular DNA hybridization was assayed by the acquisition of resistance to pancreatic ribonuclease (DNase-free RNase). Seventy-one to 75% homology was detected between Ki-MSV RNA and DNA from TR-NRK-P (NRK line transformed and productively infected with KiMSV) cells and NRK-MEV (NRK cells productively infected with MEV) cells and between MEV RNA and NRK-MEV cell DNA; these values represented the maximum level of hybridization. A low but significant degree of homology (31%) was detected between MEV RNA and NRK cell DNA, and intermediate levels of homology (42-60%) were detected between MEV RNA and NRK or TR-NRK-NP (NRK line transformed nonproductively by Ki-MSV) cell DNA and between Ki-MSV RNA and NRK or TR-NRK-NP cell DNA. The complementary spectra with NRK and TR-NRK-NP DNA with respect to either Ki-MSV or MEV RNA were quite similar, TR-NRK-NP DNA exhibiting only a slight increase in complementary sequences. It is suggested that a loss of about 30% of the genomic sequences of MEV with a concomitant gain of roughly equal amounts of rat-specific sequences in genetically stable recombinant state led to the formation of Ki-MSV.

2615 PARTIALLY SINGLE-STRANDED FORM OF FREE MOLONEY VIRAL DNA. (Eng.) Gianni, A. M. (Center Cancer Res., Massachusetts Inst. of Technology, Cambridge, Mass. 02139); Weinberg, R. A. *Nature* 255(5510):646-648; 1975.

Moloney murine leukemia viral DNA, obtained from the upper band of an ethidium bromide-cesium chloride centrifugation gradient, was characterized. Two probes were used to measure the relative amounts of the long and short strands of the viral DNA. The profile of DNA complementary to ^{125}I-RNA indicated a distribution of molecules of molecular wt 8 x 10^5 to 3 x 10^6, comparable to 1.5 x 10^6 daltons; only the largest of the first-strand DNA molecules was

equivalent in length to a complete transcript of the 35S virion RNA. The second of the proviral DNA, as detected by complementarity to ^{3}H-complementary DNA (^{3}H-cDNA) sedimented molecules of 5 x 10^5 daltons; the largest had a molecular wt of about 9 x 10^5. The proviral DNA derived from the upper band was not derived from the super-coiled closed-circular DNA. Boiling before hybridization increased the number of sites available to hybridize to ^{125}I-RNA by a factor of 1.5; prior denaturation increased the hybridization of proviral DNA to ^{3}H-cDNA. Treatment with S_1 nuclease confirmed the observation that the first-strand DNA contained sites available for hybridization by virtue of their single-strandedness. Further experiments indicated that about half of the first-strand DNA was initially found in a single-stranded state, while the second strand DNA was virtually all in a double-stranded configuration. Further confirmation was obtained by isopycnic centrifugation of the complex on sodium iodide gradients, indicating the presence of large amounts of single-stranded DNA in the proviral DNA.

2616 GENETIC CONTROL OF ONCOGENESIS BY MURINE SARCOMA VIRUS MOLONEY PSEUDOTYPE. I. GENETICS OF RESISTANCE IN AKR MICE. (Eng.) Colombatti, A. (Inst. of Pathological Anatomy, Univ. of Padova, Italy); Collavo, D.; Biasi, G.; Chieco-Bianchi, L. *Int. J. Cancer* 16(3):427-434; 1975.

The differential susceptibility to M-MSV in hybrids of AKR mice was studied. Injection (im, thigh) of Moloney mouse sarcoma virus (M-MSV) in adult mice of several inbred strains revealed that all strains except AKR are highly susceptible (80-100%) to M-MSV tumor development. F1 hybrids between AKR and CBA, DBA/2 or NIH mice are as resistant (93%) as the parental AKR strain, which indicates that resistance is transmitted as a dominant character. First backcross mice to the susceptible parent show a 3:1 ratio of resistant to susceptible mice. This is the expected ratio for two segregating loci which independently confer resistance. The incidence of resistant F2 mice is somewhat lower than expected. Further support for the two-gene hypothesis was obtained in second backcross mice. The major genes affecting murine leukemia virus infection (Fv-2 and H-2) do not seem to play any role in this system and no linkage was found with Thy.1 and albino, dilute, agouti and brown markers.

2617 GENETIC CONTROL OF ONCOGENESIS BY MURINE SARCOMA VIRUS MOLONEY PSEUDOTYPE. II. A DOMINANT EPISTATIC SUSCEPTIBILITY GENE. (Eng.) Colombatti, A. (Inst. of Pathological Anatomy, Univ. of Padova, Italy); Collavo, D.; Biasi, G.; Chieco-Bianchi, L. *Int. J. Cancer* 16(3):435-441; 1975.

The tumor response pattern of F_1, F_2, and backcross hybrids between resistant AKR and susceptible strains (C57Bl/6, BALB/c, and BIOBR) of mice following injection with the Moloney mouse sarcoma virus (M-MSV) was studied. Fv-1 typing was determined by progeny testing using the Friend virus spleen focus assay, and a humoral cytotoxic assay on peripheral leukocytes was performed for the detection of H-2^k haplotype. Among adult hybrids between AKR and B6, BALB, or BIOBR, 86% developed tumors within ten days after M-MSV injection; this was nearly the same percentage as was observed in the susceptible parents. Segregation was observed in the first backcross (Bc1) and F_2 mice, and the segregation ratios up to Bc3 mice fit a one-gene model. In tests in which susceptible F_1 hybrids were mated with a third nonparental strain, 48% of the progeny were susceptible, indicating that in some strains and their hybrids a dominant epistatic gene was masking the resistant phenotype. Progeny testing for Fv-1 showed no close linkage between susceptibility and H-2, although a slight suggestion of linkage with albino phenotype was found in F_2, but not Bc1, mice. The data conclusively indicate that M-MSV tumor induction is under host genetic control. At least three genes appear to govern the tumor response in the offspring of crosses with AKR mice: two dominant autosomal loci independently confer resistance to M-MSV tumor development in AKR; and a dominant autosomal epistatic gene masks the resistant phenotype in some individuals. There is also some evidence that additional factors may exist which exert a minimal influence on tumor response.

2618 EXPRESSION OF MOUSE MAMMARY TUMOR VIRAL POLYPEPTIDES IN MILKS AND TISSUES. (Eng.) Noon, M. C. (Natl. Cancer Inst., Bethesda, Md.); Wolford, R. G.; Parks, W. P. *J. Immunol.* 115(3):653-658; 1975.

A 14,000-dalton polypeptide (p14) from RIII murine mammary tumor virus (MMTV) was isolated by column chromatography in 6 M GuHCl. Antiserum prepared in rabbits specifically precipitated ^{125}I-labeled p14; in double antibody competition, radioimmunoassays performed with limiting amounts of antibody, both purified p14 and disrupted MMTV, competed specifically with labeled antigen. The expression of this MMTV type B virus antigen could be measured by competition radioimmunoassays in milks, mammary glands, tumors, and tissue culture cells. MMTV expression measured by p14 immunoassay correlated well with the spontaneous incidence of mammary adenocarcinomas in different murine strains but not with type C MuLV p30 antigen expression. Levels of MMTV gp52, the major type-B viral glycoprotein, corresponded to p14 levels, suggesting that their control is comparably regulated. Evidence that this low molecular weight polypeptide is present in feral and inbred strains of widely differing geographic origin and in MMTV with apparently different biologic properties suggests surprising conservation of MMTV protein homology.

2619 MOUSE MAMMARY TUMOR VIRUS POLYPEPTIDE PRECURSORS IN INTRACYTOPLASMIC A PARTICLES. (Eng.) Smith, G. H. (Natl. Cancer Inst., Bethesda, Md. 20014); Lee, B. K. *J. Natl. Cancer Inst.* 55(2):593-496; 1975.

Intracytoplasmic A particles were analyzed by immunodiffusion and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) before and

after enzymatic cleavage with trypsin. The particles were purified from transplantable Leydig cell tumors. Mouse mammary tumor virus (MMTV) was isolated from C3H-A^{vy}/He mammary tumors by sequential rate zone sedimentation in two linear gradients. A common antigen in A particles was detected by antisera prepared against this virus and against a purified MMTV core polypeptide (p28) and purified intracytoplasmic A particles. Despite this correlation, no SDS-polyacrylamide band migrating at p28 was observed in purified intracytoplasmic A particles. However, after incubation with trypsin (1.25 μg/100 μg A particle protein, 30 min, 37 C), A particles subjected to SDS-PAGE produced only two polypeptide bands. They were observed at p28 and p15-10. Ouchterlony analysis of the trypsin-cleaved A particles revealed no alteration in the antigenicity of the particles. These results suggest that some structural components of intracytoplasmic A particles are polypeptide precursors of MMTV core proteins.

2620 PROPERTIES OF A CHICKEN LYMPHOBLASTOIO CELL LINE FROM MAREK'S DISEASE TUMOR. (Eng.) Nazerian, K. (Reg. Poult. Res. Lab., Agric. Res. Serv., East Lansing, Mich.); Witter, R. L. *J. Natl. Cancer Inst.* 54(2):453-458; 1975.

Properties of a chicken lymphoblastoid cell line (MSB-1) from a Marek's disease tumor (MD) are described. MBS-1 cells were cultured at 41 C and 37 C; subcultures were made every 48 hr. MSB-1 cells died after the sixth subculture at 37 C, but were growing rapidly eight months after culturing at 41 C. They measured 8-10 μ in diameter, had a smooth surface with round nuclei which stained pink with Wright's stain. Secondary monolayers of duck embryo fibroblasts (DEF) or chick embryo fibroblasts (CEF) exhibited microplaques typical of MD-virus after 6-7 days of co-cultivation with 1×10^3 to 2.5×10^5 MSB-1 cells. In virus-producing cells, the nuclear chromatin was marginated, nucleoli were fragmented and naked nucleocapsids appeared in the nucleus. Ten chicks (7_2 line) were inoculated ip with 24 plaque-forming units (PFU) of MSB-1 cells; all developed tumors in the pectoral muscle (3/10 died). Two of five untreated chicks kept in the same cage developed similar tumors. All of nine chicks, inoculated ip with 310 PFU of DEF (co-cultivated with MSB-1 cells), and two of five untreated chicks in the same cage developed visible pectoral muscle tumors. Controls failed to develop tumors. These results demonstrate that co-cultivation of MSB-1 with DEF or CEF results in the transfer of the disease agent to these cells.

2621 EFFECTS OF CYCLOHEXIMIDE ON VIRUS ONA REPLICATION IN AN INOUCIBLE LINE OF POLYOMA-TRANSFORMED RAT CELLS. (Eng.) Manor, H. (Dept. Biology Technion-Israel Inst. Technology Haifa, Israel); Neer, A. *Cell* 5(3):311-318; 1975.

The biochemical transformations causing induction of virus synthesis in an inducible polyoma-transformed rat cell line (LPT) was studied by analyzing the effect of cycloheximide (CH) on the replication of viral DNA in the repressed and activated states. At a concentration of 10 μg/ml, CH had two distinct effects on the replication of polyoma virus (PV). Exposure of LPT cells to CH caused up to an 8-fold increase in the cellular concentration of PV DNA determined by molecular hybridization. The treatment also inhibited cell division and chromosomal DNA replication, but did not affect the amount of chromosomal DNA per cell. In LPT cells treated with mitomycin C (1 μg/ml), PV DNA replication was enhanced after seven hours. Between 7-24 hr, the concentration of virus DNA increased at least 100-fold. CH added to the cells 0-7 hr after treatment with mitomycin C inhibited the replication of PV DNA by 90-100%. The inhibition was less effective in cells exposed to CH from 7 hr and on. The inhibitory effect was reversible: virus DNA synthesis was resumed after removal of CH from the growth medium. The data indicate that CH acts as an inducer of virus DNA synthesis in cells whose resident viral genome is repressed, but inhibits the autonomous replication of the activated genome following induction with MMC. At least two proteins (or groups of proteins) apparently control the replication of PV DNA; one directly or indirectly involved in maintaining the repressed state of the viral genome, and the other playing an essential role in the autonomous replication of PV DNA.

2622 TEMPERATURE-OEPENDENT PROPERTIES OF CELLS TRANSFORMEO BY A THERMOSENSITIVE MUTANT (TS-121) OF POLYOMA VIRUS. II. CHARACTERIZATION OF 121-6 CELLS. (Eng.) Okada, Y. S. (Res. Inst. for Microbial Diseases, Osaka Univ., Suita, Osaka, Japan); Hakura, A. *Int. J. Cancer* 16(3):394-403; 1975.

The growth and agglutinability properties of a cell line transformed by a temperature-sensitive mutant of polyoma virus (ts-121) in liquid media were studied. The cell lines used were: A31-714, a recloned cell line from BALB/3T3 cells; PV-4, a line of A31-714 cells transformed by wild-type polyoma virus; and 121-6-5, a subclone isolated from 121-6 (a transformed line induced by ts-121). Determinations were made of cell density and agglutinability by concanavalin A (Con A); autoradiography was performed after treatment with 5 μCi/ml of ^{3}H-thymidine. The cells were grown at 35 or 39 C. Both the morphology and saturation density of the 121-6 cells were affected by temperature; at 39 C, they grew to monolayer sheets and remained contact inhibited for at least 25 days, while at 35 C, they grew beyond the monolayer density, thus resembling the PV-4 cells. When the cells were incubated at 39 C and the temperature was shifted to 35 C before the cells became confluent, they continued to grow beyond the saturation density normally reached at 39 C. However, when they were downshifted after reaching confluence, they began to grow only after a 34 day latent period. When sparse cultures were moved from 35 to 39 C, they continued to grow to form a monolayer; when cultures which had grown beyond confluence were similarly upshifted, growth stopped and a gradual decrease in cell density was observed.

The agglutinability of the 121-6-5 cells was not temperature-dependent; even at high temperatures, these cells showed a high agglutinability. The data suggest that the agglutinability by plant lectin may not be directly correlated with other phenotypic markers of transformants, such as the changes in cell morphology and saturation density.

2623 AMPLIFICATION OF A SPECIFIC REGION OF THE POLYOMA VIRUS GENOME. (Eng.) Griffin, B. E. (Imperial Cancer Res. Fund, PO Box 123, Lincoln's Inn Fields, London WC2A 3PX, England); Fried, M. *Nature* 255(5514):175-179; 1975.

Defective DNAs, isolated from mouse cells after infection with a clonally purified stock of defective polyoma virus, were characterized and studied in detail. Heteroduplex studies showed the region of homology between this defective DNA and wild type DNA molecules to begin on the latter about 16% from the *Escherichia coli* RI restriction enzyme single cleavage site. To locate the homology region on the polyoma physical map and define the defective DNAs and related defective species more precisely, a restriction enzyme analysis was performed. Cleavage of the defective DNAs with HhaI (from *Haemophilus haemolyticus*) produced only one fragment (about 17% wild-type genome length) that was not similar in size to any of the three fragments produced from wild type DNA. Treatment of the defective DNAs with HpaII in incomplete digestion conditions produced one predominant partial digestion product, which corresponded in length to about 17% of the wild-type genome. No partial digestion products less than 17% were detected, suggesting that in these DNAs there is a basic subunit which is tandemly repeated either 2, 3, 4, 5, or 6 times to produce the different defective species. The defective DNAs and their HpaII cleavage products were also treated with a restriction enzyme from *Haemophilus aegyptius* (HaeIII). The results of the restriction enzyme analysis defined the viral sequences in the 17% subunit as extending from HpaII-3 through HpaII-5 into HpaII-4 on the polyoma physical map. Assuming only viral sequences to be present, and knowing the order and approximate size of the HaeIII fragments of the wild-type DNA in this region, it is estimated that of the sequences in the 17% subunit, 18-27% come from HpaII-3 and 42-53% come from HpaII-4. These sequences come from the region of the viral DNA that contains the origin of DNA replication and the 5' ends of early and late stable messenger RNAs. The apparent uniformity of the repeating subunit suggests that the defective DNA and related molecules are derived from the subunit by recombination events.

2624 DEOXYRIBONUCLEIC ACID-BINDING PROTEINS IN VIRUS-TRANSFORMED CELL LINES. (Eng.) Melero, J. A. (Departamento de Biologia Molecular, Instituto B. Maranon, Centro de Investigaciones Biologicas, C.S.I.C., Velazquez, 144. Madrid-6, Spain); Salas, M. L.; Salas, J.; Macpherson, I. A. *J. Biol. Chem.* 250(10):3683-3689; 1975.

The synthesis of proteins with affinity for DNA was studied in clones of a Syrain hamster cell line (NIL) and subclones of this line transformed by polyoma virus (NIL-Py) or hamster sarcoma virus (NIL-HSV). The synthesis of DNA-binding proteins in NIL and in its virus-transformed derivatives, NIL-Py and NIL-HSV, was very similar in exponentially growing cells, but in dense culture there was a very significant difference in the level of a protein (P8), which was much higher in the transformed lines than in untransformed NIL. Experiments with synchronized cells indicated that the time of maximal P8 synthesis relative to cellular DNA synthesis in NIL-HSV precedes that observed in NIL cells. P8 has a molecular weight of 30,000 as determined by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate and is present in large amounts in the transformed cells in dense culture, where it makes up 0.5 to 1% of the total soluble protein. It is concluded that P8 is greatly reduced in dense NIL cells, but is prominent in dense transformed cells. The fact that the high levels in the latter were observed in all the clones of NIL-HSV indicates that this behavior is due to the transformed state, and not to fortuitous clonal selection.

2625 DETECTION OF TYPE A ONCORNAVIRUS-LIKE STRUCTURES IN CHICKEN EMBRYO CELLS AFTER INFECTION WITH ROUS SARCOMA VIRUS. (Eng.) Maul, G. G. (Wistar Inst. Anatomy and Biology, Philadelphia, Pa. 19104); Lewandowski, L. J.* *J. Virol.* 16(4):1071-1074; 1975.

Occasional aggregates of high electron-dense particles were observed within the cytoplasm of chicken embryo cells transformed by Rous sarcoma virus (RSV). A clone-purified stock of subgroup C of RSV was used to infect C/E chicken embryo cells, which were incubated with and without 20 μM glucosamine/ml for 16 hr. Thin sections of cells were then stained with uranyl acetate and studied with the electron microscope. The particles were present in approximately 10% of all cells and appeared to be composed of membrane-free nucleoids resembling type A oncornavirus, with diameters of about 60.0 nm, and electron-lucent centers of about 25.0 nm surrounded by two dense rings. The aggregates were not glycogen because the uranyl acetate stain would have leached glycogen, and they were not lysosomes because they were not surrounded by a membrane. Complete and incomplete core-like structures with electron-lucent centers were also seen in unstained preparations. These particles were not detected in noninfected cells, and they did not accumulate in excess under conditions of glucosamine block. It is suggested that the particles may be either newly synthesized viral cores or infecting virus actively engaged in virus replication.

2626 ABSENCE OF SURFACE PROJECTIONS ON SOME NON-INFECTIOUS FORMS OF RSV. (Eng.) de Giuli, C. (Rockefeller Univ., New York, N. Y. 10021); Kawai, S.; Dales, S.; Hanafusa*, H. *Virology* 66(1):253-260; 1975.

Purified virus particles of two strains of Rous sarcoma virus that are defective in glycoprotein synthe-

sis were examined with the electron microscope to determine if there is a correlation between the absence of glycoproteins and the absence of surface projections. Chicken embryo cells either positive or negative for both the group-specific antigen and endogenous helper factor were used. Primary or secondary chicken cells, from either helper factor-negative or -positive embryos, were infected with the defective mutant of the Schmidt-Ruppin strain of Rous sarcoma virus or the Bryan high-titer strain of Rous sarcoma virus that had been propagated in helper-negative cells in the presence of 25 μg/ml of diethylaminoethyl dextran and 1,500 hemagglutinating U/ml of UV-inactivated Sendai virus. The cultures were transferred at 4- to 5-day intervals until the entire culture consisted of only transformed cells. The virus shed into the medium was harvested, purified by centrifugation through a sucrose gradient, and examined by electron microscopy following negative staining with 2% phosphotungstic acid. The viruses defective in formation of virion glycoproteins, were seen to be lacking in projections if they were propagated in helper factor-negative cells, but they had projections when they were replicated in helper factor-positive cells. The defective sarcoma viruses were noninfectious when grown in helper factor-negative cells. It is suggested that the glycoproteins residing on the projections are essential for the interaction with cellular receptors to permit initiation of the infectious process. Although virions without projections are incapable of penetrating the cells, they appear to become adsorbed to the host cell surface at almost the same rate as infectious types, indicating that the projection is not necessary for the adsorption step.

2627 COMPARISONS OF MAJOR CELL-SURFACE PROTEINS OF NORMAL AND TRANSFORMED CELLS. (Eng.) Robbins, P. W. (Cent. Cancer Res., Massachusetts Inst. Technol., Cambridge). *Am. J. Clin. Pathol.* 63 (5):671-676; 1975.

Transformation of the chick fibroblast surface was studied in cells infected with Schmidt-Ruppin Rous sarcoma virus and its temperature sensitive mutant, TS-68. Transformation caused a dramatic decrease in the levels of these cellular proteins: Z (molecular weight 230,000), Ω (206,000), and Δ (47,000). TS-68-infected cells were pulse-labeled with ^{35}S-methionine. When they were transferred from 41 C to 36 C they stopped synthesizing the Ω protein. The intracellular location of this protein is not known. The rate of synthesis of Δ protein dropped to 10-20% of the 41 C rate within 3-6 hr after the TS-68 infection culture was shifted to 36 C. This change in concentration was not due to increased proteolysis or turnover. When the TS-68-infected cells were maintained at the permissive temperature for an extended time and then shifted to 41 C, increased synthesis began promptly. The exact physiologic role of Δ, a plasma membrane protein, is unknown. It is suggested that it is a structural component that governs or restrains general plasma membrane protein mobility. There was a cessation or slowing of the synthesis of the large trypsin- and collaginase-sensitive protein, Z, but only after days of morphological transformation by TS-68 virus. The concentration of collaginase necessary for 50% degradation of Z was three times higher than for trypsin, and was correlated to stimulated deoxyglucose transport. However, the breakdown of Z was not essential for activating fibroblasts, as the Vmax of thrombin was 10-fold lower to stimulate deoxyglucose uptake than that causing 50% breakdown of Z. The significance of Z in growth control is uncertain. Generally, the TS-68-infected cells differed by increased quantities of type-specific viral antigen in the membranes at 41 C, as compared to 36 C.

2628 PARTIAL PURIFICATION AND CHARACTERIZATION OF DNA POLYMERASES FROM A ROUS SARCOMA VIRUS-TRANSFORMED RAT CELL LINE. (Eng.) Bandyopadhyay, A. K. (N.C.I. Frederick Cancer Res. Center, Frederick, Md. 21701). *Biochim. Biophys. Acta* 407(1): 1-13; 1975.

A new DNA polymerase was partially purified from cell-free extracts of a continuous rat cell line (XC). The XC cells had been transformed by the Prague strain of Rous sarcoma virus but did not produce infectious virus. The molecular wt of the DNA polymerase is 70,000, as estimated by glycerol gradient centrifugation and by Sephadex gel filtration. This enzyme can be distinguished from the other cellular DNA polymerases by its elution pattern on DNA-cellulose column chromatography, its molecular wt, and its primer-template specificity. The enzyme has some characteristics of the murine leukemia virus reverse transcriptase. It is partially inhibited by immunoglobulin G (IgG) purified from rabbit antiserum prepared against Rauscher leukemia virus reverse transcriptase, but it is not inhibited by IgG from rat antiserum prepared against avian myeloblastosis virus reverse transcriptase. However, the XC cell enzyme can be distinguished from the murine leukemia virus reverse transcriptase by its inefficiency in copying an oligo-$(dG)_{12}$·poly(rC)primer-template.

2629 CHARACTERIZATION OF DEFECTIVE SV40 ISOLATED FROM SV40-TRANSFORMED CELLS. (Eng.) Huebner, K. (Wistar Inst. Anat. Biol., Philadelphia, Pa.); Santoli, D.; Croce, C. M.; Koprowski, H. *Virology* 63(2):512-522; 1975.

Defective simian virus 40 (SV40) virions isolated from SV40-transformed monkey, human, and hamster cell lines that had failed to yield wild type virus after Sendai virus-mediated fusion with permissive African green monkey kidney TC7 cells were characterized. KBr-purified pools were processed in several ways: (1) A sample was inoculated into TC7 cell cultures, and coverslips were examined for SV40-induced T or V antigens; (2) An aliquot was centrifuged to equilibrium in CsCl solution, and fractions were assayed for density and total radioactivity; and (3) An aliquot of DNA was extracted and analyzed by ethidium bromide CsCl centrifugation and by velocity sedimentation in neutral CsCl for the presence of closed circular double-stranded DNA. The bouyant densities in CsCl of the defective viruses ranged between 1.32 and 1.33 g/cc.

The DNA isolated from defective viruses was heterogenous in size and contained some covalently closed double-stranded circular molecules. These data indicate that defective virion preparations rescued from the nonrescuable transformed cell lines contain DNA of the size and conformation of SV40 component I DNA. Although defective viruses isolated from nonrescuable transformed monkey, human, and hamster cells were capable of replication to a limited extent (as evidenced by the formation of microplaques on TC7 monolayers and by the incorporation of radioactive precursors into virion DNA and protein), the defective viruses had a reduced ability to induce detectable levels of viral antigens in permissive, semipermissive, and nonpermissive cells. T antigen-positive mouse cell clones, established after infection with a defective virus stock rescued from H50 cells, did not have the characteristics of wild type SV40-transformed cells (except that they were T antigen-positive) and were presumably nontransformed. Recovery of defective viruses from these transformed cell lines is consistent with the proposal that cells that are permissive or semipermissive to SV40 lytic infection and that survive SV40 lytic infection to become transformed contain defective viral genomes.

2630 UV-INDUCED REVERSION OF A TEMPERATURE-SENSITIVE LATE MUTANT OF SIMIAN VIRUS 40 TO A WILD-TYPE PHENOTYPE. (Eng.) Cleaver, J. E. (Lab. Radiobiology, Univ. California, San Francisco, Calif. 94143); Weil, S. *J. Virol.* 16(1):214-216; 1975.

UV radiation (50 ergs/mm^2/sec of 254-nm light for 1-7 min) of a simian virus 40 temperature-sensitive late mutant before infection of CV1 monkey cells produced viruses that were phenotypically wild-type revertants (calculated from the ratio of the number of plaques formed on infected monolayers at 39 C) was high, and increased approximately as the square of the UV dose. The revertants grew at 39 C, but were more sensitive than the temperature-sensitive mutant to heating at 60 C. The revertants produced by UV light must therefore be suppressor mutations rather than reversions of the original temperature-sensitive mutant; this may explain the relatively high frequency of the UV-induced reversion. It is suggested that suppression may involve second-site mutations in the viral genome in a manner similar to that previously seen in spontaneous revertants isolated from a simian virus 40 temperature-sensitive mutant.

2631 PRODUCTION OF LYMPHOKINE-LIKE FACTORS (CYTOKINES) BY SIMIAN VIRUS 40-INFECTED AND SIMIAN VIRUS 40-TRANSFORMED CELLS. (Eng.) Bigazzi, P. E. (Sch. of Medicine, 327 Sherman Hall, State Univ. of New York at Buffalo, Buffalo, N. Y. 14214); Yoshida, T.; Ward, P. A.; Cohen, S. *Am. J. Pathol.* 80(1):69-78; 1975.

Macrophage migration inhibitory (MIF-like) activity was demonstrated in the supernatant fluids from primary cultures of African green monkey kidney cells infected with simian virus 40 (SV40). Virus-free kidney cell cultures had no MIF activity. Supernatant fluids from continuous cultures of nontransformed and SV40-transformed human fibroblasts contained MIF-like activity. Productive infection with SV40 virus results in the production of a lymphokine-like factor. SV40 infection does not induce chemotactic factors. The results reported here, taken in conjunction with previous observations, suggest that the production of lymphokine-like factors (cytokines) may be a general biologic phenomenon, and that many, if not all, cell types may be capable of such activity.

2632 QUANTITATIVE MEASUREMENT OF SV 40 T-ANTIGEN PRODUCTION. (Eng.) Horan, M. (Los Alamos Sci. Lab., Univ. California, N.M.); Horan, P. K.; Williams, C. A. *Exp. Cell Res.* 91(2):247-252; 1975.

African green monkey cells (CV-1) were infected with simian virus 40 (SV40) virus at high multiplicities of infection (MOI), and the production of T-antigen was studied. A new instrumentation, flow microfluorometry, coupled with indirect immunofluorescence permitted quantitative evaluation of this antigen. Optimum conditions were determined for antibody excess. Antigen production was not detected for the first six hours post-infection. The value of this technology is discussed in relation to quantitative evaluation of expression of cellular antigens. By permitting comparison of antigen production rates among various strains of SV40 and the study of conditions that might alter these rates, the technology could yield valuable information on the control of virus infection.

2633 SIMIAN VIRUS 40 DNA DIRECTS SYNTHESIS OF AUTHENTIC VIRAL POLYPEPTIDES IN A LINKED TRANSCRIPTION-TRANSLATION CELL-FREE SYSTEM. (Eng.) Roberts, B. E. (Biol. Dep., Massachusetts Inst. Technol., Cambridge); Gorecki, M.; Mulligan, R. C.; Danna, K. J.; Rozenblatt, S.; Rich, A. *Proc. Natl. Acad. Sci. USA* 72(5):1922-1926; 1975.

The characteristics and requirements of a linked cell-free system capable of transcribing and translating mammalian viral DNA are described. The system is a heterologous one utilizing *Escherichia coli* RNA polymerase to transcribe the DNA template and wheat germ extracts to translate the RNA into protein. Simian virus 40 (SV40) DNA Form I (supercoiled) directed the synthesis of discrete polypeptides up to 85,000 daltons in size. One of these products was indistinguishable from authentic major virus capsid protein VPI, as judged by motility on sodium dodecyl sulfate/polyacrylamide gels, antibody precipitation, and peptide analyses. The cell-free products larger than VPI comprised a number of polypeptides ranging in molecular weight from 50,000 to 85,000. These polypeptides demonstrated no immunological relationship to the structural protein VPI. However, two of these products, along with one of approximately 25,000 daltons, were precipitated with antiserum to SV40 tumor antigen. Linear SV40 DNA generated by the cleavage of Form I DNA with the restriction endonuclease *Eco*R$_1$ was an efficient template in this system and also

directed the synthesis of a polypeptide migrating with VPI on polyacrylamide gels. This cell-free system should facilitate the identification of exclusively virus-coded polypeptides, the direct mapping of viral DNA, the study of control mechanisms regulating the flow of information from DNA into polypeptides, and, in combination with hybridization techniques, the purification of specific eukaryotic genes. With SV40, the use of restriction enzyme DNA fragments or DNA from homogeneous defective populations as templates will facilitate functional mapping of the viral genome.

2634 TOPOGRAPHY OF SUBSTRATE-ATTACHED GLYCOPROTEINS FROM NORMAL AND VIRUS-TRANSFORMED CELLS. (Eng.) Culp, L. A. (Sch. Medicine, Case Western Reserve Univ., Cleveland, Ohio 44106). *Exp. Cell Res.* 92(2):467-477; 1975.

The topographical distribution of substrate-attached materials (SAM) which may mediate adhesion of BALB/c 3T3 and SV40-transformed 3T3 cells to the culture substrate was studied. Autoradiographic detection of these 'glycoproteins' on the substrate after incorporation of ^{14}C-glucosamine or ^{35}S-methionine indicated: glucosamine-labeled SAM on the substrate of confluent cultures was evenly distributed, the methionine content of SAM from transformed cells was deficient, after these materials were directly deposited onto the substrate at cell colony locations, and not randomly on the substrate secretion into the medium. Autoradiographic detection of these 'glycoproteins' subsequent to ^{3}H-glucosamine (or ^{3}H-leucine) incorporation and exposure to liquid emulsion indicated that substrate-attached glycoproteins were present in focal pools on the underside of the cell, and that these focal pools were distributed comparably, in terms of number of foci per area of substrate, for confluent normal and transformed cells. The patterns of SAM deposited by freshly-attaching and spreading 3T3 cells have also been examined. The evidence suggests that cells are adherent to the substrate at localized areas which appear to be evenly distributed on the underside of normal or transformed cells.

2635 MAPPING OF THE SV40 SPECIFIC SEQUENCES TRANSCRIBED *IN VITRO* FROM CHROMATIN OF SV40 TRANSFORMED CELLS. (Eng.) Astrin, S. M. (Inst. for Cancer Res., Fox Chase Cancer Center, Philadelphia, Pa. 19111). *Biochemistry* 14(12):2700-2704; 1975.

Chromatin was isolated from simian virus 40 (SV40)-transformed mouse cells (SV3T3) and transcribed with *Escherichia coli* RNA polymerase. The SV40 specific transcripts were analyzed by annealing the RNA to the minus strands of purified fragments of SV40 DNA produced by cleavage of the DNA with a restriction enzyme isolated from *Hemophilus aegyptius*. Quantitation of the frequency of transcription from the regions represented by the fragments showed that the early region (fragments A and D) was transcribed 5-10 times more frequently than the remaining regions. These results are in good agreement with the transcription pattern observed in the transformed cell. In contrast, transcription of purified SV3T3 DNA by *E. coli* polymerase produced roughly equal frequencies of transcription from all regions of the integrated SV40 DNA. Comparison of the results with the known distribution of initiation sites for *E. coli* RNA polymerase on linear SV40 DNA indicates that the major initiation site is relatively unavailable in SV3T3 chromatin whereas other sites are available. This restriction is not observed when purified SV3T3 DNA is used as a template and must therefore result from the association of protein or other macromolecules with the DNA of the chromatin.

2636 SOMATIC CELL HYBRIDS BETWEEN MOUSE PERITONEAL MACROPHAGES AND SIMIAN-VIRUS-40-TRANSFORMED HUMAN CELLS: II. PRESENCE OF HUMAN CHROMOSOME 7 CARRYING SIMIAN VIRUS 40 GENOME IN CELLS OF TUMORS INDUCED BY HYBRID CELLS. (Eng.) Croce, C. M. (Wistar Inst. Anat. Biol., Philadelphia, Pa.); Aden, D.; Koprowski, H. *Proc. Natl. Acad. Sci. U.S.A.* 72(4):1397-1400; 1975.

A study was undertaken to determine if the human chromosome 7 carrying the Simian virus 40 (SV40) genome and coding for SV40 T antigen is present in cells derived from tumors induced in 'nude' mice by injecting hybrid cells. A heterogeneous population of hybrid cells with 14 different human chromosomes and a quasi-tetraploid number of mouse chromosomes was injected sc into 20 BALB/c 'nude' mice at 2×10^{7} to 4×10^{7} cells per mouse. Tumor-derived cells obtained were transfered 5-8 times in culture and stained for presence of SV40 T antigen. Karotypic analysis was performed by Giemsa banding. Human chromosome 7 was the only chromosome present in 100% of the metaphases examined. 'Nude' 8, 1, and 9 tumor sources contained only human chromosome 7. When five mice were implanted with fragments of tumor 9, even after culture passages, all contained tumors with SV40 T antigen. These results indicate that somatic cell hybrids between normal and SV40-transformed cells behave as transformed cells *in vitro*, and that the transformed phenotype is dominant. The human chromosome 7 carries the SV40 genome that codes for "transforming factors". It may be possible to identify the human chromosome responsible for expression of tumor phenotype in human malignancies.

2637 DETECTION OF VIRUS-SPECIFIC DNA SEQUENCES BY QUANTITATIVE *IN SITU* HYBRIDIZATION DURING INFECTION WITH SV40. (Eng.) Langelier, Y. (Faculte de Medecine, Universite de Sherbrooke, Sherbrooke, Quebec, Canada); Mandeville, R.; Simard, R. *Int. J. Cancer* 16:476-487; 1975.

In situ hybridization was tested for use as a quantitative method to study the replication of simian virus 40 (SV40) DNA during lytic infection of monkey kidney cells (CV-1 or BSC-1). Baby hamster kidney cells and Cl_2TSV_5, a clone of hamster cells transformed by SV40, were also studied. [^{3}H]thymidine-labeled viral DNA was used as a template to synthesize [^{3}H]cRNA, which was used in the *in situ* hybridization experiments. The effects of various

fixation and denaturation procedures on hybrid formation were determined, as was the timing and [^{3}H]-cRNA concentration required for maximum hybrid formation. To determine whether *in situ* hybridization could be used as a quantitative method for the detection of multiple DNA sequences in infected cells, the time course of DNA synthesis in infected cells was studied and the correlation between the input multiplicity of infection and the number of infected cells was compared. Finally, attempts were made to demonstrate viral genome(s) in Cl_2TSV_5 metaphase and interphase cells. The results indicated that when all parameters were carefully controlled and the same preparation of [^{3}H]cRNA was used, the system gave results with a reproducibility of $\pm$10%. Maximum hybrid formation was obtained using methanol/acetic acid fixation and formamide denaturation, the optimum [^{3}H]cRNA concentration was 0.2 μg/ml, and a maximum of 75% of the cells were significantly labeled after a reaction time of 4-5 hr. The data further indicated that the synthesis of viral DNA was not localized in a special area of the nucleus and that it was not synchronized in confluent cells. Moreover, about 20-30% of the cells are not labeled, whatever the multiplicity of infection. It was not possible to detect the integrated genome in the Cl_2TSV_5 cells, due either to the small size of the genome or to the fact that the number of genome-equivalents integrated at the same place was too low to yield a radioactivity superior to the background level for long periods of exposure. The method may, however, prove extremely useful for larger viruses.

2638 TRANSCRIPTION OF SIMIAN VIRUS 40. V. REGULATION OF SIMIAN VIRUS 40 GENE EXPRESSION. (Eng.) Laub, O. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel); Aloni*, Y. *J. Virol.* 16(5):1171-1183; 1975.

The biogenesis of the viral RNAs found late after infection was studied in BSC-1 cells infected with simian virus 40 (SV40) strain 777. RNA "exhaustion type" hybridization was used to measure the complementarity of nuclear and cytoplasmic viral RNA to the early (E) and late (L) SV40 DNA strands. This type of hybridization measures the amount of labeled RNA complementary to each of the two DNA strands. At 48 hr after infection, about 5% of the nuclear newly synthesized viral RNA was complementary to the E-strand and 95% was complementary to the L-strand. This proportion remained constant for labeling times of 2 min to several hr, and indicated similar accumulation of the E- and L-RNA transcripts in the nucleus. The nuclear E- and L-viral RNA transcripts sedimented in a similar manner on sucrose gradients. Of the cytoplasmic viral RNA about 1% was complementary to the E-strand; these molecules sedimented at 19S and 16S. The abundance of E-RNA transcripts in nuclei of cells infected with serially passaged virus was about four times higher than that in nuclei of cells infected with plaque-purified virus. The size and proportion of the corresponding cytoplasmic E- and L-RNA transcripts was independent of the type of virus used to infect the cells. These results suggest that control of strand selection occurs mainly at the transcriptional level and that the choice of specific fragments ultimately transported to the cytoplasm occurs after transcription.

2639 PURIFICATION OF R-DNA POLYMERASE FROM AN ADENOVIRUS DNA REPLICATION COMPLEX [abstract]. (Eng.) Arens, M. Q. (St. Louis Univ., Mo.); Ito, K.; Yamashita, T.; Green, M. *Fed. Proc.* 34(3): 494; 1975.

2640 SULFATED COMPONENTS OF ENVELOPED VIRUSES. (Eng.) Pinter, A. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021); Compans, R. W. *J. Virol.* 16(4):859-866; 1975.

2641 STUDIES OF EPSTEIN-BARR VIRUS NUCLEAR ANTIGEN AND ANTISERA USING A QUANTITATIVE MICRO COMPLEMENT FIXATION ASSAY [abstract]. (Eng.) Baron, D. (Harvard Univ., Cambridge, Mass.); Benz, W. C.; Strominger, J. L. *Fed. Proc.* 34(3):527; 1975.

2642 PRESENCE OF AN AUTOCOMPLEMENTARY RNA WITH VIRAL SPECIFICITY IN HERPES VIRUS-INFECTED CELLS. (Fre.) Bechet, J.-M. (Unite d'Oncologie Virale, Institut Pasteur, 25, rue de Docteur-Roux, 75015 Paris, France); Montagnier, L. *C.R. Acad. Sci. [D] (Paris)* 280(2):217-220; 1975.

2643 THE ROLE OF GENITAL HERPES VIRUS IN CANCER OF THE UTERINE CERVIX. (Fre.) Thiry, L. (Departement de Virologie, Institut Pasteur du Brabant, Bruxelles, Belgium); Sprecher-Goldberger, S. *Bull. Acad. Med. Belg.* 129(1):109-141; 1975.

2644 DETECTION OF VIRAL CORES HAVING TOROID STRUCTURES IN EIGHT HERPESVIRUSES. (Eng.) Nii, S. (Res. Inst. Microb. Dis., Osaka Univ., Japan); Yasuda, I. *Biken J.* 18(1):41-46; 1975.

2645 A HERPESVIRUS-TYPE AGENT ASSOCIATED WITH SKIN LESIONS OF GREEN SEA TURTLES IN AQUACULTURE. (Eng.) Rebell, G. (Sch. Medicine, Univ. of Miami, Miami, Fla. 33152); Rywlin, A.; Haines*, H. *Am. J. Vet. Res.* 36(8):1221-1224; 1975.

2646 POLYADENYLATION OF HERPES SIMPLEX VIRUS RNA [abstract]. (Eng.) Swanstrom, R. I. (Univ. California, Irvine); Pivo, K. R.; Wagner, E. K. *Fed. Proc.* 34(3):526; 1975.

2647 TUBULAR STRUCTURES IN RABBIT KIDNEY CELLS INFECTED WITH *HERPESVIRUS CUNICULI*. (Eng.) Nii, S. (Res. Inst. for Microbial Diseases, Osaka Univ., Yamadi-kami, Suita, Osaka, Japan); Yasuda, I. *Biken J.* 18(2):145-148; 1975.

2648 INFECTIOUS SPREAD AND CONTROL OF FELINE LEUKEMIA VIRUS. (Eng.) Hardy, W. D., Jr. (Memorial Sloan-Kettering Cancer Center, New York, N.Y.); McClelland, A. J. *Transplant. Proc.* 7(2):265-267; 1975.

2649 DEMONSTRATION OF FELINE LEUKEMIA VIRUS ANTIBODY IN CATS BY PASSIVE HEMAGGLUTINATION. (Eng.) Wang, J. T. (New York State Veterinary Coll., Cornell Univ., Ithaca, N.Y. 14850); Lee, K. M. *Proc. Soc. Exp. Biol. Med.* 148(2):557-561; 1975.

2650 EFFECT OF 1-β-D-RIBOFURANOSYL-1,2,4-TRIAZOLE-3-CARBOXAMIDE (RIBAVIRIN) ON FRIEND LEUKEMIA VIRUS INFECTIONS IN MICE. (Eng.) Sidwell, R. W. (Nucleic Acid Res. Inst., Irvine, Calif. 92664); Allen, L. B.; Huffman, J. H.; Witkowski, J. T.; Simon, L. N. *Proc. Soc. Exp. Biol. Med.* 148(3):854-858; 1975.

2651 CONTINUOUS REPLICATION OF FRIEND VIRUS COMPLEX (SPLEEN FOCUS-FORMING VIRUS-LYMPHATIC LEUKEMIA-INDUCING VIRUS) IN MOUSE EMBRYO FIBROBLASTS: RETENTION OF LEUKEMOGENICITY AND LOSS OF IMMUNOSUPPRESSIVE PROPERTIES. (Eng.) Eckner, R. J. (Boston Univ. Sch. Medicine, Boston, Mass. 02118). *J. Exp. Med.* 142(4):936-948; 1975.

2652 EFFECT OF DIETHYLAMINOETHYL-DEXTRAN ON THE REPLICATION OF A MURINE SARCOMA (MOLONEY)-LEUKEMIA VIRUS COMPLEX IN MOUSE EMBRYO CULTURES. (Eng.) Hirschman, S. Z. (Mount Sinai Sch. Medicine of City Univ. of New York, New York, N.Y. 10029); Funke, V. *Proc. Soc. Exp. Biol. Med.* 148(2):527-531; 1975.

2653 CHARACTERIZATION OF ENDOGENOUS RNA-DIRECTED DNA POLYMERASE ACTIVITY OF RETICULOENDOTHELIOSIS VIRUSES. (Eng.) Kang, C.-Y. (Univ. of Texas Southwestern Medical Sch., Dallas, Tex. 75235). *J. Virol.* 16(4):880-886; 1975.

2654 BIOLOGY OF MOUSE RNA TUMOR VIRUSES. (Jpn.) Takano, T. (Keio Univ. Med. School, Tokyo, Japan). *Tampakushitsu Kakusan Koso* 20(2):140-150; 1975.

2655 STUDY OF THE EFFECT OF STORAGE ON ROUS SARCOMA VIRUS. (Rus.) Zelenskii, V. P. (All-Union Scientific Res. Inst. of Avian Diseases, USSR); Laretskaia, L. I.; Rozhnova, L. I.; Rachkovskaia, L. A. *Veterinariia* (8):36; 1975.

2656 CONCENTRATION OF ROUS SARCOMA VIRUS FROM TISSUE CULTURE FLUIDS WITH POLYETHYLENE GLYCOL. (Eng.) Bronson, D. L. (Univ. of Minnesota Health Sciences, Minneapolis, Minn. 55455); Elliott, A. Y.; Ritzi, D. *Appl. Microbiol.* 30(3):464-471; 1975.

2657 HUMAN PAPOVAVIRUS-BK DNA: CHARACTERIZATION AND POLYNUCLEOTIDE SEQUENCE HOMOLOGY TO SV40 DNA [abstract]. (Eng.) Howley, P. M. (Natl. Inst. Allergy Infect Dis., Bethesda, Md.); Khoury, G.; Takemoto, K. K.; Mullarkey, M. F.; Martin, M. A. *Fed. Proc.* 34(3):526; 1975.

2658 CLONING AND AMPLIFICATION OF SPECIFIC DEFECTIVE GENOMES OF SV40 [abstract]. (Eng.) Ganem, D. (Harvard Med. Sch., Boston, Mass.); Davoli, D.; Fareed, G. C. *Fed. Proc.* 34(3):526; 1975.

2659 METHYLATED SV40-SPECIFIC RNA FROM NUCLEI AND CYTOPLASM OF INFECTED BSC-1 CELLS [abstract]. Lavi, S. (Roche Inst. Mol. Biol., Nutley, N.J.); Shatkin, A. J. *Fed. Proc.* 34(3):526; 1975.

2660 BIOLOGICAL ACTIVITIES OF CLONED EVOLUTIONARY VARIANTS OF SIMIAN VIRUS 40 [abstract]. (Eng.) Brockman, W. W. (Johns Hopkins Univ. Sch. Med., Baltimore, Md.); Scott, W. A. *Fed. Proc.* 34(3):526; 1975.

2661 *IN VITRO* SYNTHESIS OF RNA IN ISOLATED NUCLEI FROM SIMIAN VIRUS 40 INFECTED CELLS [abstract]. (Eng.) Qasba, P. K. (Natl. Cancer Inst., Bethesda, Md.); Yi, P.-N.; Finlayson, B. *Fed. Proc.* 34(3):526; 1975.

2662 CELL-MEDIATED CORRECTION OF MISMATCHED BASES IN HETERODUPLEX MOLECULES OF SIMIAN VIRUS 40 DNA [abstract]. (Eng.) Lai, C.-J. (Johns Hopkins Univ. Sch. Med., Baltimore, Md.); Nathans, D. *Fed. Proc.* 34(3):515; 1975.

2663 ADENYLATE CYCLASE OF NORMAL AND TRANSFORMED HUMAN FIBROBLASTS: INFLUENCE OF HORMONES AND 2-CHLOROADENOSINE [abstract]. (Eng.) Makman, M. H. (Albert Einstein Coll. Med., New York, N.Y.); Keehn, E. *Fed. Proc.* 34(3):264; 1975.

See also:

* (Rev): 2412, 2413, 2414, 2435, 2436
* (Chem): 2470, 2474
* (Immun): 2665, 2668, 2669, 2671, 2673, 2675, 2680, 2687, 2688, 2690, 2701, 2703, 2705, 2709, 2710, 2742, 2747, 2752,
* (Path): 2783, 2807
* (Epid): 2882, 2901, 2909

2664 HUMORAL AND CELLULAR IMMUNE REACTIONS *'IN VITRO'* AGAINST ALLOGENEIC AND AUTOLOGOUS HUMAN MELANOMA CELLS. (Eng.) Peter, H. H. (Department of Clinical Immunology, Medizinische Hochschule, Postfach 180, D-3000 Hannover-Kleefeld, West Germany); Kalden, J. R.; Seeland, P.; Diehl, V.; Eckert, G. *Clin. Exp. Immunol.* 20(2):193-207; 1975.

Based on ^{51}Cr release from an allogeneic human melanoma cell (M1) cell-mediated (CMC) and antibody-dependent cellular cytotoxicity (ADCC) were determined in 28 melanoma patients, 31 healthy controls, ten patients with other tumors and 11 chronic lymphocytic leukemia (CLL) patients. The results were based on simultaneously performed microcytotoxity (MC) tests, HL-A typing, plasma membrane fluorescence and B:T cell ratios in the peripheral blood. Furthermore, lymphocytes from six melanoma patients were tested in CMC and ADCC assays against autologous cells. Fifteen out of 34 CMC tests performed with normal lymphocytes yielded more than 15% isotope release as compared to seven out of 40 tests in the melanoma group; many healthy controls also possessed lymphocytes which readily lysed M1 target cells in MC assays. CMC activity of lymphocytes from melanoma patients was generally lower than than of control lymphocytes and decreased further with progression of the disease. CLL lymphocytes were virtually nontoxic for M1 cells, even at high aggressor target cell ratios. ADCC assays with a heterologous rabbit-anti-M1 serum showed generally higher isotope release than CMC assays; this was particularly pronounced in the melanoma group and in the group of patients with other tumors. No tumor-specific blocking factor could be detected in melanoma sera, as judged by the capacity of the sera to block CMC activity. No obvious correlation was found between short-term CMC and long-term MC assays. E-rosette formation revealed that T lymphocyctes were significantly diminished in melanoma patients. The HL-A type of lymphocytes from normal donors and melanoma patients did not appear to be related to high or low activity in CMC and MC assays. Preliminary results of ^{51}Cr release tests with autologous melanoma cells were encouraging with respect to the correlation of the results to the clinical course of the disease.

2665 HOST REACTIVITY TO BOVINE PAPILLOMA VIRUS-INDUCED FIBROBLASTOMAS. (Eng.) Barthold, S. W. (Univ. Wisconsin, Madison). *Diss. Abstr. Int. B.* 35(9):4721-4722-B; 1975.

Active bovine papilloma virus (BPV) was studied in calves. Pieces of BPV-inoculated dermis were transplanted to eight calves. Transformation did not occur around tissue that received the dermis after 72 hr. Sera from six calves with BPV-induced tumor contained antibody to cultured fibroma cells. Twelve calves were challenged with BPV and were susceptible to the virus; after the onset of fibroma regression, complete resistance to challenge occurred. The use of indirect immunofluorescence demonstrated the presence of cross-reacting membrane neoantigens on bovine and equine BPV-induced tumor cells, but not on normal cells.

2666 EFFECT OF MULTIPLE INJECTIONS OF ALLOGENEIC SPLEEN CELLS ON METHYLCHOLANTHRENE CARCINOGENESIS IN THE MOUSE. (Eng.) Oth, D. (Unite INSERM, U 95, Plateau de Brabois, 54500 Vandoeuvre-les-Nancy, France); Liegey, A. *Biomedicine* 23(1): 17-19; 1975.

Mice were pretreated with allogeneic transplantation antigens in an attempt to diminish the establishment of primary tumors induced by methylcholanthrene (MCA, 0.1 mg). The mice were treated with 10^6 spleen cells, sc, weekly for seven weeks. In all experiments, allogeneic spleen cells (type 1, origin of spleen cells changed every week) treatment diminished the number of tumors in comparison with untreated controls (91/123 or 73% and 121/135 or 90%, respectively). Mean survival time of the tumor-bearing animals was not influenced by the treatment. When the allogeneic cell donors were always of the same strain (type 2 spleen cells), no protection was observed. These data suggest that immunoprophylaxis occurs as a result of pretreatment of mice with allogeneic spleen cells of multiple origin against MCA carcinogenesis.

2667 CELLULAR IMMUNOLOGIC RESPONSIVENESS TO EXTRACTS OF OVARIAN EPITHELIAL TUMORS. (Eng.) Melnick, H. (Lenox Hill Hosp., New York, N. Y.); Barber, H. R. K. *Gynecol. Oncol.* 3(1):77-86; 1975.

The leukocyte migration inhibition assay was employed in an investigation of cellular immunological reactivity to a solubilized extract of pooled, epithelially derived ovarian carcinomas. Lymphocyte-rich populations of leukocytes were prepared from heparinized blood of patients having primary ovarian cancers and of various control subjects. The epithelial extract was prepared from fresh surgical specimens of serous and mucinous cystadenocarcinomas of the ovary. In 85% of patients having adenocarcinoma of the ovary, leukocyte migration was 30-77% inhibited in the presence of the ovarian tumor extract in the assay. Leukocytes obtained from patients having endometroid, mesometanephric, and teratocarcinomas of the ovary were not inhibited by incubation with the epithelial ovarian extract. similar absence of migration inhibition was observed in patients with squamous cell carcinoma of the cervix, endometrial carcinoma, i.e., malignant tumors other than seromucinous adenocarcinomas. A lack of migration inhibition was also noted in leukocytes obtained from patients with various benign ovarian neoplasms from normal or pregnant females, or from normal males. It is suggested that the demonstrated cellular immunologic reactivity to a specific ovarian epithelial tumor antigen may serve as an approach to an early diagnostic test for histologically specific types of ovarian cancer.

2668 MAREK'S DISEASE IN IMMUNOSUPPRESSED CHICKENS: GROWTH OF A TRANSPLANTABLE LYMPHOMA AND DEVELOPMENT OF THE DISEASE BY NATURAL EXPOSURE. (Eng.) Cotter, P. F. (Dep. Pathobiol., Univ. Connecticut, Storrs); Jakowski, R. M.; Fredrickson, T. N.; Schierman, L. W.; McBride, R. A. *J. Natl. Cancer Inst.* 54(4):969-973; 1975.

The effect of treatment of syngeneic White Leghorn chickens with Cytoxan (CY) on immunocompetence and on susceptibility to Marek's disease (MD) was investigated. Chicks were immunosuppressed by intraabdominal injections of CY shortly after hatching, or at two-three wks of age. Immunocompetence was tested by survival of allogeneic,full-thickness skin grafts and by humoral response to injected sheep red blood cells (SRBC), virus. Exposure to MD was effected either by s.c. inoculation of the left wing web or by forced-air contact with MDV-infected birds. The incidence of wing web lymphomas in chicks treated with CY at hatching was 100%, as in saline-treated controls; further, no anti-SRBC hemagglutinins were detected in 96% of the CY-treated chicks, while skin graft survival was not affected. In assessing the immunocompetence of chicks treated with CY at two-three wk, however, hemagglutinins were detected and titers were highest in chicks receiving 37 and 75 mg CY/kg weight. Only chicks receiving 150 mg CY/kg had a delayed rejection time to allogeneic skin grafts and significantly fewer bursa-dependent foci observable on midsaggital spleen sections. Thus CY treatment at hatching produced almost complete unresponsiveness to antigenic stimulation and affected primarily the humoral immune system. However, later CY immunosuppression resulted in a dose-dependent enhancement or suppression of anti-SRBC antibody production, and only a slight increase in skin graft survival time.

2669 EVALUATION OF THE CELL-MEDIATED IMMUNE RESPONSE TO MURINE SARCOMA VIRUS BY [^{125}I]-IODODEOXYURIDINE ASSAY AND COMPARISON WITH CHROMIUM 51 AND MICROCYTOTOXICITY ASSAYS. (Eng.) Fossati, G. (Natl. Cancer Inst., Bethesda, Md. 20014). Holden, H. T.; Herberman, R. B. *Cancer Res.* 35(9):2600-2608; 1975.

The cell-mediated immune response of C57BL/6 mice to murine sarcoma virus (MSV) was examined by the [^{125}I]-iododeoxyuridine ([^{125}I]IUdR) release cytotoxicity assay using MSV-induced sarcoma tissue culture cell lines as target cells. Cellular cytotoxicity was detected as early as three days after virus inoculation. Most mice assayed between 12 and 17 days after MSV inoculation im gave positive results with maximum levels of activity present on days 13 and 14. Reactivity was frequently detected for up to 100 days after MSV inoculation, although at low levels (5 to 10%). Additional experiments comparing the kinetics of the cellular response as measured by different *in vitro* cytotoxicity assays were performed. The results showed a good direct correlation between the [^{125}I]-IUdR release assay and a ^{51}Cr release assay. A similar pattern of reactivity was also observed when the cellular response was measured by a visual microcytotoxicity assay, although reactivity dropped off more rapidly and became undetectable in most instances by 20 days after injection of MSV. Studies on effector cell type revealed that cytotoxicity in all three assays was T-cell dependent, being eliminated by treatment with anti-θ plus complement. Macrophages did not appear to play a role, since treatment with carbonyl iron and magnet had no effect. It is suggested that additional testing against other target cells is indicated.

2670 CELL-MEDIATED IMMUNITY TO MURINE TUMOR ALLOGRAFTS. INCREASE IN THE ACTIVITIES OF ACTIVATED THYMUS-DERIVED CELLS FOLLOWING *IN VITRO* INCUBATION. (Eng.) Gorczynski, R. M. (Ontario Cancer Inst., 500 Sherbourne St., Toronto, Ontario M4X 1K9, Canada); Tigelaar, R. E. *Cell. Immunol.* 18(1):121-143; 1975.

The immunity of C57Bl spleen cells to an allogeneic mastocytoma, P815, was studied with a direct cytotoxicity assay and an assay of macrophage migration inhibition. Spleen cells, obtained from C57Bl mice given P815 cells (10×10^6) cells 18 days before, were separated by velocity sedimentation into large and small cell fractions. Irradiated (850 rads) C57Bl mice, divided into groups of six mice each, were inoculated with these cells or unfractionated cells. At 24 hr postinoculation, spleens and peripheral lymph nodes were pooled within each group; aliquots were then tested for their activity in cytotoxic lymphocyte (CL) and migration inhibition factor (MIF) assays. The CL activity of unfractionated immune spleen cells showed a marked preference for migration to the spleens rather than lymph nodes of recipients, while the MIF cell activity showed no such preferential migration to the spleen. Both large CL and MIF cells showed a marked preference for migration to the spleen, while small CL and MIF cells gave rise to activity in both spleens and lymph nodes of recipients. Overnight incubation in the absence of deliberately added antigen substantially increased CL and MIF activity of immune spleen cells and resulted in the detection of MIF activity in small cells that were initially inactive. The activity in each assay was abolished by pretreatment of immune cells with rabbit antimouse brain-associated θ serum (anti-BAθ) and guinea pig complement, and no new activity was seen after overnight incubation in anti-BAθ serum. Thus, the increase in activity after incubation in the absence of antigen depended on the existence of T cells in the initial culture. Short-term exposure to trypsin (100 μg/ml) depressed the MIF activity of large T cells, but increased the activity of small cells. Increases in CL activity and the development of MIF activity from small cells could be blocked by incubation in the presence of serum from spleen cell donors. These results suggest that blocking factors exist on the surface of some small T lymphocytes taken from P815 immune C57Bl mice, and that these factors can suppress T cell activity in both of the assay systems used.

2671 VIRAL WARTS, HERPES SIMPLEX AND HERPES ZOSTER IN PATIENTS WITH SECONDARY IMMUNE DEFICIENCIES AND NEOPLASMS. (Eng.) Morison, W. L. (St. John's Hosp., Leicester Square, London, England). *Br. J. Dermatol.* 92(6):625-630; 1975.

The incidence of viral warts, recurrent herpes simplex, and herpes zoster was assessed in 633 patients with possible secondary immune deficiency states and in 348 control subjects. The 633 patients included 78 with multiple myeloma, 159 with Hodgkin's disease, 109 with malignant lymphoma, 51 with chronic lymphatic leukemia (CLL), 156 with systemic malignancy, and 80 with cutaneous basal cell carcinoma. The pa-

tients and controls were over 17 yr old. The subjects were interviewed and all lesions were examined Compared with the controls, the incidence of warts was increased in patients with Hodgkin's disease (29.6%), malignant lymphoma (20.1%), and CLL (17.6%) In contrast to these patients with cell-mediated immune deficiency, patients with humoral immune deficiency did not show an increased incidence of warts. The incidence of herpes zoster infection was also higher in patients with Hodgkin's disease (28%), malignant lymphoma (25%), and CLL (28%) than in other patient groups. The increase of warts in the Hodgkin's-lymphoma-leukemia group was not due to treatment (chemotherapy or radiotherapy), because the increased incidence was noted before treatment. However, treatment may have been an influence on the higher incidence of herpes zoster. Recurrent herpes simplex infection was not increased in patients with cell-mediated or humoral immune deficiencies. This study suggests that cell-mediated immunity may be important in both the prevention and resolution of infections due to wart virus, and in preventing infections due to varicella-zoster virus. However, immunologic factors are not important in preventing herpes simplex infections.

2672 INHIBITION OF PROLIFERATION OF LYMPHOMA CELLS AND LYMPHOCYTES BY SUPPRESSOR CELLS FROM SPLEENS OF TUMOR-BEARING MICE. (Eng.) Kirchner, H. (Natl. Cancer Inst., Bethesda, Md.); Muchmore, A. V.; Chused, T. M.; Holden, H. T.; Herberman, R. B. *J. Immunol.* 114(1):206-210; 1975.

Spleen cells, obtained from C57Bl/6N mice injected im with 0.05 ml of Moloney murine sarcoma virus (MSV) to induce tumor, were mixed with syngeneic normal spleen cells or with RBL-5 lymphoma cells to study the inhibition of DNA synthesis by MSV spleen cells. MSV spleen cells were cultured in RPMI 1640 supplemented with 5% fetal bovine serum, 100 u/ml penicillin, 100 μg/ml streptomycin, and 2 mM glutamine for 72 hr. MSV spleen cells (3×10^5) inhibited [^{3}H]thymidine (TdRH3) uptake of phytohemagglutinin-stimulated normal spleen cells (5×10^5) when MSV-cells had no prior treatment (87% inhibition of TdRH3 uptake), and upon prior treatment with 2,500 R X-irradiation (83% inhibition). This inhibition was not seen upon prior treatment with 400 μg/ml Carrageenan (13% inhibition) or passage through Rayon adherence columns (5% inhibition). MSV cells inhibited TdRH3 uptake of RBL-5 cells at 10:1 ratios (6,738 counts/min uptake *versus* 185,316 counts/min by controls), while normal spleen cells enhanced uptake (260,271 counts/min). DNA synthesis (as measured by TdRH3 uptake) is inhibited by MSV spleen cells. The suppressor cells from MSV spleens demonstrate the characteristics common to macrophages (i.e. inhibition by Carrageenan and removal by Rayon adherence columns).

2673 ACTIVATION OF C-TYPE VIRUSES DURING SKIN GRAFT REJECTION IN THE MOUSE. INTERRELATIONSHIPS BETWEEN IMMUNOSTIMULATION AND IMMUNOSUPPRESSION. Hirsch, M. S. (Mass. Gen. Hosp., Boston); Ellis, D. A.; Kelly, A. P.; Proffitt, M. R.; Black, P. H.; Monaco, A. P.; Wood, M. L. *Int. J. Cancer* 15(3):493-502; 1975.

Both mouse-tropic and zenotropic C-type RNA viruses were activated in BALB/c mice during rejection reactions against skin grafts from mice differing at the major histocompatibility locus (A/J) or sharing this locus (DBA/2). Animals that maintained their skin grafts following immunosuppression with antilymphocyte serum (ALS, 0.25 ml ip twice weekly for two wk beginning the day after grafting and 0.1 ml twice weekly thereafter) or cyclophosphamide (20 mg/kg/day ip from day of grafting; a total dose of 560 mg/kg) had a much higher incidence of virus-positivity than animals that did not receive ALS or cyclophosphamide, or that rejected their skin grafts despite immunosuppressive therapy. ALS itself activated type-C viruses from a small proportion of BALB/c mice whereas cyclophosphamide alone did not. Type-C viruses were detected in spleens and regional nodes draining skin-graft sites between one and two wk following transplantation; thereafter they reached maximum titers in spleens. Viruses were not detected at skin-graft sites, in tails, or in thymuses of grafted animals. Virus activation was associated with splenic histological changes consisting of germinal center formation, diffuse hyperplasia of reticulum cells, depletion of periarteriolar lymphocytes and hyperplasia of red pulp hematopoietic elements. These results suggest that detection of C type virus activation following immunostimulation reactions may depend on persistent immunosuppression following the induction event.

2674 EFFECT OF WATER-SOLUBLE ADJUVANTS ON *IN VITRO* LYMPHOCYTE IMMUNIZATION. (Eng.) Sharma, B. (Sch. Med., Univ. California, Los Angeles); Kohashi, O.; Mickey, M. R.; Terasaki, P. I. *Cancer Res.* 35(3):666-669; 1975.

Evidence for the potentiation of lymphocyte transformation and *in vitro* immunization by water-soluble adjuvants (WSA) from *Mycobacterium smegmatis* and human mixed mycobacteria strains is presented. Lymphocytes purified over Ficoll-Hypaque were immunized *in vitro* by culturing with mitomycin C-treated tumor cells, and cytotoxic activity was tested using a ^{51}Cr release assay. Lymphocyte transformation by WSA did not occur in the range of 5-40 μg/ml; however, one-way MLCs were amplified by WSA. An increase in thymidine incorporation was generally observed as the WSA concentration was increased to 40 μg/ml; the average uptake increased significantly ($72 \pm 14\%$). *In vitro* immunization of lymphocytes to cultured human tumor cells revealed a significant amplification in response against breast, lung, Hep-2, and bladder tumor cell lines in the presence of WSA. Lymphocyte response to phytohemagglutinin (PHA) was depressed in the presence of WSA. The data suggest that WSA produce amplification of the MLC response in approximately the same range as produced by polyadenylic acid and polyuridylic acid. WSA may be useful in boosting immunization of lymphocytes *in vitro*.

2675 A KILLED VACCINE DERIVED FROM THE ONCOGENIC *HERPESVIRUS ATELES*. (Eng.) Laufs, R. (Hygiene-Institut der Universitat Gottingen, D-34 Gottingen, West Germany); Steinke*, H. *J. Natl. Cancer Inst.* 55(3):649-651; 1975.

A killed herpesvirus vaccine was prepared by inactivation of the oncogenic Herpesvirus ateles (HVA) with heat and formaldehyde. The vaccine was used safely in marmosets (Saguinus oedipus) for 461 days. The vaccinated marmosets developed high titers of serum antibodies against HVA and were resistant to 316 lethal dose 50 (LD50) cell-free HVA. The nonvaccinated control monkeys died of malignant lymphoma. The five challenged monkeys were clinically well and were under observation for 362 days without signs of HVA infection. A nonhuman primate species can be successfully vaccinated against malignant lymphoma induced by cell-free HVA. The prevention of malignant lymphoma with a killed HVA vaccine supports the concept that HVA is the etiologic agent for the tumors observed in the nonvaccinated control monkeys. The induction of a cellular immune response remains to be determined. It seems possible to develop an HVA vaccine free of viral nucleic acid similar to that being used to protect against Marek's lymphomas in chickens.

2676 VARIANTS OF A MOUSE MYELOMA CELL LINE THAT SYNTHESIZE IMMUNOGLOBULIN HEAVY CHAINS HAVING AN ALTERED SEROTYPE. (Eng.) Preud'Homme, J. L. (Albert Einstein Coll. Med., Bronx, N. Y.); Birshtein, B. K.; Scharff, M. D. *Proc. Natl. Acad. Sci. USA* 72(4):1427-1430; 1975.

A selected group of MPC-11 mouse myeloma cell variants having serological, chemical, and assembly characteristics of a different subclass from the parent was described. The cell lines were derived from the MPC-11 mouse myeloma tumor, which produces an IgG_{2b} immunoglobulin. These different lines were subjected to *in vitro* mutagenesis with ICR-191 or Melphalan and subsequent cloning in soft agar. The resulting clones were overlaid with rabbit antibody against the Fc region of the MPC-11 H chain, and those not covered by a visible precipitate were selected for mass culture. The presence of heavy chains was detected by Ouchterlony analysis of cytoplasmic lysates and secreted immunoglobulins using antisera to the MPH-11 chain and its fragments and antisera directed against other mouse subclasses. Molecular weights of H chains were determined by electrophoresis of radiolabeled immunoglobulin molecules on acrylamide gels containing sodium dodecyl sulfate. The variants were also subjected to peptide analysis by ion exchange chromatography. The Ouchterlony analyses showed that where H chains of normal size were produced by variants, such chains were not recognized by antiserum against the parental IgG_{2b} serotype, but rather were recognized by an antiserum against the IgG_{2a} subclass. Four variants synthesizing H chains of the γ2a subclass possessed chains of normal size (55,000 molecular weight) and one synthesized a γ2a subclass H chain of 75,000 molecular weight. When the variants and the parent were compared using antibody against the Fc region of the MPC-11 protein, spurs of incomplete identity were seen, indicating that the variants lacked antigenic determinants present in the parent chain. An antiserum directed against the Fab region of the MPC-11 protein failed to distinguish variants from the parent. Further, the γ2a variants lacked many of the tryptic/chymotryptic peptides found in the parent, contained tryptic/chymotryptic peptides not present in the parent but present in an unrelated γ2a myeloma chain, and assembled with light chains by a pathway typical of IgG_{2a} myelomas. A suggested nonmutational mechanism was the turning off of one gene and the turning on of another. Mutational mechanisms suggested involved mitotic crossing over or deletion involving parts of neighboring γ2b and γ2a genes.

2677 IMMUNOGLOBULINS UNDER THE INFLUENCE OF NONSPECIFIC FACTORS. II. THE INFLUENCE OF WORK-STRESS ON LEVELS OF IMMUNOGLOBULINS (IgG, IgA, IgM) OF MINERS IN URANIUM MINES. (Eng.) Wagner, V. (Inst. Health Uranium Ind., Pribram, Czechoslovakia); Andrlikova, J.; Palek, V. *Z. Immunitaetsforsch.* 148(4):356-365; 1975.

Serum IgG, IgA, and IgM levels were measured before and after the workshift in two groups of 22 miners each, exposed 5.4 and 10.8 yr, respectively, to the environment of an underground uranium mine. The average age was 30.5 yr in the first group and 36.95 yr in the second. Immunoglobulin levels were determined by radial immunodiffusion. After the workshift, miners with the longer exposure showed a significant decrease in all three immunoglobulin classes; in miners with the shorter exposure, only IgG decreased significantly. Initial IgG levels were considerably lower in miners exposed for ten years compared with those with shorter exposure. Differences in the decreases of immunoglobulin levels between the two groups were significant only in the case of IgA. This study shows that the stress of a single workshift in uranium mines decreases immunoglobulin levels, and that this decrease differs with the length of previous exposure and, apparently, with age of the miners.

2678 DETECTION OF ANTIBODY AND COMPLEMENT COMPLEXED *IN VIVO* ON MEMBRANES OF HUMAN CANCER CELLS BY MIXED HEMADSORPTION TECHNIQUES. (Eng.) Irie, K. (Cent. Health Sci., Univ. California, Los Angeles); Irie, R. F.; Morton, D. L. *Cancer Res.* 35(5):1244-1248; 1975.

The mixed hemadsorption (MHA) techniques were used to demonstrate antibody and complement fixed *in vivo* to the surface of human cancer cells. Tumors from twelve cancer patients and normal tissues from five cancer patients and eight patients with cerebrovascular or cardiac diseases were collected from biopsy and autopsy for *in vitro* testing. Antiserum to human whole immunoglobulins and antiserum to human complement 3 (C3) were used in the MHA techniques. Positive MHA patterns were demonstrated on the surface of cancer cells by both methods. Positive reactions ranged from 12 to 32% in mixed hemadsorption for

antibody detection and from 10 to 34% in mixed hemadsorption for C3 detection. Normal tissues obtained from cancer patients or from patients who died of causes other than cancer rarely exhibited distinct MHA reactivity. Collectively, the data suggest that most human cancers are antigenic in the autologous host and that tumor-associated antigens of cancer cells react *in vivo* with their humoral antibody to fix complement.

2679 REACTIVITY OF SMOOTH-MUSCLE ANTIBODIES, SURFACE ULTRASTRUCTURE, AND MOBILITY IN CELLS OF HUMAN HEMATOPOIETIC CELL LINES. (Eng.) Fagraeus, A. (Natl. Bacteriological Lab., Stockholm, Sweden); Nilsson, K.; Lidman, K.; Norberg, R. *J. Natl. Cancer Inst.* 55(4):783-789; 1975.

Seventeen human hematopoietic cell lines were tested by indirect immunofluorescence (IF) for reactivity with human serum containing smooth-muscle antibodies (SMA). The correlation of the IF pattern to the cell surface ultrastructure was revealed by scanning electron microscopy (SEM). Lymphoma cells, viewed by SEM, had short villi over the entire cell surface, but, by IF, showed membrane fluorescence. Cells of lymphoblastoid lines had thin, long, surface villi, sometimes asymmetric but most often distributed over the whole cell surface. Myeloma and leukemia cells, which had few membrane villi but a surface covered by "blebs" revealed by SEM, demonstrated, by IF, only a few stub-like projections extending from the surface. Time-lapse cinematography revealed a positive correlation between long, thin, surface villi demonstrated by IF and SEM and the degree of motility. Indirect IF with human SMA-positive serum might be used in the classification of cell lines derived from human hematopoietic tissue.

2680 CLONAL NATURE OF THE IMMUNE RESPONSE TO PHOSPHORYLCHOLINE (PC). V. CROSS-IDIOTYPIC SPECIFICITY AMONG HEAVY CHAINS OF MURINE ANTI-PC ANTIBODIES AND PC-BINDING MYELOMA PROTEINS. (Eng.) Claflin, J. L. (Washington Univ. Sch. Med., St. Louis, Mo.); Davie, J. M. *J. Exp. Med.* 141(5): 1073-1083; 1975.

To test the implication that a prerequisite for all phosphorylcholine (PC)-combining activity in mice is a heavy chain subtype, PC-binding myeloma proteins and anti-PC antibodies from different mouse strains were studied using a cross-idiotypic assay. Seven mouse myeloma proteins with specificity for PC were found to share a common antigenic determinant. This group of proteins contained members which differed in genetic origin, heavy chain class, κ-chain subgroup, individual antigenic determinants, and specificity for choline analogues. The cross-idiotypic determinant, designated V_H-PC, was antigenically similar in each of the proteins, and was associated with the variable portion of the heavy chain in the region of the antibody combining site. Further studies showed that an indistinguishable determinant was present on IgM anti-PC antibodies isolated from all strains of mice tested, regardless of histocompatibility or heavy chain allotype. In view of the finding that this cross-idiotypic determinant was not found on antibodies or myeloma proteins that lacked specificity for PC, the data suggest that a particular heavy chain variable region is preserved in all mouse antibodies with specificity for PC.

2681 EFFECT OF TRANSPLANTED SYNGENEIC MYELOMAS ON THE ANTIBODY RESPONSE OF MICE. (Eng.) Warr, G. W. (Univ. Med. Sch., Edinburgh, Scotland); Willmott, N.; James, K. *Eur. J. Cancer* 11(5):351-357; 1975.

Antibody responses to alum precipitated bovine serum albumin (BSA) and sheep erythrocytes (SRBC) in mice bearing various syngeneic myelomas were investigated. Inbred BALB/c mice of both sexes, age 10-12 weeks, were used. Standard immunizing doses of 1 mg BSA in alum or 3×10^8 SRBC in 0.3 ml were injected i.p., and the antibody response was assessed by antigen-binding capacity and relative binding affinity. The growth of all of the myelomas significantly depressed the antibody response to alum BSA, while the relative binding affinity of the antibody produced was not reduced by the growth of any tumor. The splenic PFC response to SRBC in mice simultaneously transplanted with viable tumor varied, however, as follows. During early tumor growth, melanomas MOPC 47A, MPC 25, and ADJPC 5 significantly depressed the IgG1 response, while MOPC 47A also suppressed the IgG2b response and ADJPC 5 also suppressed the IgG2a response. The IgM response was unaffected by the early growth of melanomas MOPC 47A, MPC 25, and ADJPC 5, while it was enhanced by melanoma MOPC 104EM. During late growth of all of the tumors, the IgM response was unaffected, all IgG subclass responses were unaffected by MPC 25 or MOPC 104EM, MOPC 47A enhanced all of IgG subclass responses, and ADJPC 5 enhanced the IgG1 response. No indication of the influence of the class of Ig secreted by the melanomas on the effects of the myelomas on the class of PFC produced were noted. While the failure of established myelomas to suppress the primary IgG response to SRBC was thus observed, the manner of their depressing effects on humoral immune response to alum BSA was not clear.

2682 THE MITOGENIC ACTIVITY OF POLYADENYLIC-POLYURIDYLIC ACID COMPLEXES. (Eng.) Han, I. H. (Univ. Michigan Med. Sch., Ann Arbor); Johnson, A. G. *Ann. N.Y. Acad. Sci.* 249:370-379; 1975.

The capacity of polyadenylic and polyuridylic acid complexes (poly A:U) in increasing antibody synthesis to a number of different antigens was investigated. BALB/Aj mice were inbred and used throughout the study. Single cell suspensions were prepared from spleens, mesenteric lymph nodes, and thymuses, and labeled with [^{3}H]thymidine. Mice were killed by cervical dislocation; the spleen was removed, homogenized, and cultured. By 24 hr, the cells given antigen alone showed a 38% increase in [^{3}H]thymidine incorporation; poly A:U alone produced a 24% increase, while combined stimulation of poly A:U and antigen effected a 150% increase. Poly A:U alone was as mitogenic as SRBC. *In vivo* effects

were studied *via* administration of poly A:U. Two days after injection, 260% stimulation was observed, with similar values in animals receiving poly A:U plus SRBC. The elimination of cortisone-sensitive lymphocytes did not reduce or modify the mitogenic effects of poly A:U, indicating an effect other than T_0-cells. In studying the differences in homeostatic factors related to cortisone treatment, it was found that poly A:U increased the stimulatory effect and the level of DNA synthesis. The *in vitro* effect of poly A:U on bone marrow cells resulted in a 180% increase in [^{3}H]thymidine incorporation, irrespective of the dose level or presence or absence of antigen. The results indicate that mitogenic activity by poly A:U can be demonstrated in mouse spleen cells, that such stimulatory effects on [^{3}H]thymidine incorporation can be elicited in the absence of injected antigen, and that cortisone-resistant T-cells may be responsible for the enhanced incorporation of [^{3}H]thymidine.

2683 NEW CELL SURFACE ANTIGENS IN RAT DEFINED BY TUMORS OF THE NERVOUS SYSTEM. (Eng.) Fields, K. L. (Dep. Zool., Univ. Coll., London, England); Gosling, C.; Megson, M.; Stern, P. L. *Proc. Natl. Acad. Sci. USA* 72(4):1296-1300; 1975.

S.c. injection of N-ethyl-N-nitrosourea into newborn, inbred W/FU rats resulted in tumors of the brain, cord, lumbar cord and roots, and spinal roots. Several cell lines were developed from these tumors, 13 clonal cell lines from other alkylnitrosourea-induced tumors were also used, and antisera were prepared by i.p. injection of cultured cells of rat tumor line 33B into C34/He mice. The antisera were tested mainly by a two-stage dye exclusion cytotoxicity assay. They had high cytotoxic titers (1:4000) against all rat cells tested, tumor or normal. After extensive adsorption with normal liver, spleen and thymus, the serum was not cytotoxic for thymocytes, yet killed cells of rat tumor lines 21A and 33B equally well. In contrast, absorption with line 21A cells had very little effect on the cytotoxic titer for line 33B cells. These findings, together with further analysis, defined two antigens: a common antigen shared by brain, embryonic tissue, and neural tumors, and a restricted antigen present only on a subset of neural tumors. In screening for the restrictive antigen, no normal tissues showed definite adsorption, numerous clonal cell lines tested negative, and neither brain nor embryonic tissue showed clearly detectable amounts. The restricted antigen thus separated various tumor cells into two classes.

2684 INDUCTION OF THE IMMUNE RESPONSE TO CELL SURFACE ANTIGENS IN VITRO. (Eng.) Manson, L. A. (Wistar Inst., 36th and Spruce Streets, Philadelphia, Pa. 19104); Palmer, J. C. *In Vitro* 11(4):186-204; 1975.

Immune responses to cell surface antigens were demonstrated on two tissue culture incubation systems. In the one-way "mixed lymphocyte interaction" system, a specific stimulation of thymidine uptake was induced by a particulate membrane antigen fraction, the microsomal lipoproteins (MLP), when low levels (0.01 to 0.001 μg per ml) were incubated with spleen or lymph node cells from nonsensitized mice. No stimulation was seen when allogeneic MLP was used at high levels, 10 μg per ml, nor at any level with syngeneic MLP. Specific effectors were demonstrated after 72-hr incubation with stimulatory levels of allogeneic MLP in three separate *in vitro* assays, a plaque-forming cell reduction assay, a tumor target assay, and an antigen-binding cell assay. In the latter assay, [^{125}I]MLP was used as the source of antigen. This system has limited potential as mouse spleen cells do not survive in it beyond the fourth day of culture. The second tissue culture system, the Marbrook system, has much greater possibilities because at least 25% of the inoculum is recovered seven days later. In this culture system, a cell-free sheep erythrocyte membrane preparation can induce plaque-forming cells in the absence of macrophages. Using a sensitive radioimmunoassay, free specific antibody was detected in culture supernatant fluids. With the same culture system, allogeneic lymphocytotoxic cells (killer) have been induced with spleen cells from unprimed mice in strains differing at the major histocompatibility locus (H-2). Allogeneic MLP induced very significant "killer" cell activity with spleen cells from primed mice. In a syngeneic tumor system, significant amounts of killer cell activity were induced with unprimed spleen cell inocula, and much larger amounts induced with spleen cells from immunized mice.

2685 BIOLOGIC EFFECTS OF SOLUBILIZED H-2 AND TUMOR-SPECIFIC ANTIGENS. (Eng.) Law, L. W. (Natl. Cancer Inst., Bethesda, Md.); Appella, E.; Chang, K. S. S. *Transplant. Proc.* 7(2):233-241; 1975.

The genetically well-defined histocompatibility antigens (H-antigens), specifically H-2 antigens, derived from dissociated spleen cells of A/J mice and the tumor-associated cell-surface antigens of the transplantation type (TSTA) of BALB/c mice were studied. The H-antigens and TSTA were solubilized by papain digestion and purified by G-150 Sephadex fractionation. All allogenic specificities (detected by cytotoxicity inhibition of a ^{51}Cr release assay) and transplantation antigens of H-2 were confined to fraction F2 following chromatography. All biological activity assayed (i.e., alloantigenicity, enhancing capacity, and immunogenicity) were confined to a single peak (fraction F2). Complete tolerance was not achieved; however, humoral tolerance was easily induced. No class I and II fragments were detected. In addition, β-2-like molecules were associated with alloantigenic activity. These results suggest that the H-2 antigen represents a complete molecule containing all the major determinants detected *in situ*. TSTA of neoplastic cells transformed by simian virus 40 (SV40) demonstrated immunologic activity concentrated mainly in the peak (fraction F2) that was positive for allogeneic activity. As little as 5.0 μg of crude soluble (CS) material produced protection against a challenge of 7×10^3 and 7×10^4 SV40-transformed neoplastic cells of BALB/c mice. This represents an immunogen yield of approximately 20% for CS preparations. TSTA on Rauscher-induced

leukemogenic virus (RNA oncogenic virus) in C57BL/6 mouse cells was also isolated and solubilized from RBL-2 cell membranes. Specific immunogenicity was again retained in fraction F2 which contained alloantigenic activity. Cytotoxic antisera, which demonstrated on a microcomplement fixation assay a specific component not related to structural virus proteins, was induced by RBL-5 membranes. These results suggest that the solubilized antigen of the RNA oncogenic virus-induced neoplasm is a new cellular antigen analogous to the TSTA of a DNA oncogenic virus-induced neoplasm.

2686 HL-A IN CANCER FAMILY "N". (Eng.) Lynch, H. T. (Creighton Univ. Sch. Medicine, Omaha, Nebr. 68178); Thomas, R. J.; Terasaki, P. I.; Ting, A.; Guirgis, H. A.; Kaplan, A. R.; Magee, H.; Lynch, J.; Kraft, C.; Chaperon, E. *Cancer* 36(4): 1315-1320; 1975.

HL-A typing was performed on 115 members of cancer family N, a large kindred (over 1000 members ascertained) with the cancer family syndrome. In the cancer-prone line of the family, 20 of 21 members with cancer had one HL-A haplotype, HL-A2-HL-A12 (relative odds = 6.30). In this analysis some deceased family members who had haplotypes assigned by extrapolation from their offspring and other first-degree relatives were included. Eleven of 12 family members with cancer who were actually typed had HL-A2-HL-A12 (relative odds = 6.06). The single exception showing cancer and another haplotype in branch D is a child of a family member with haplotype HL-A2-HL-A12. The association of HL-A2-HL-A12 with cancer within this family is significant ($p < 0.025$). The study also indicates that if a cancer-susceptibility gene exists, it is not expressed in all members.

2687 EXPRESSION OF VIRUS-ASSOCIATED ANTIGENS AND IMMUNE CELL FUNCTIONS DURING SPONTANEOUS REGRESSION OF THE FRIEND VIRAL MURINE LEUKEMIA. (Eng.) Cerny, J. (Harvard Sch. Public Health, Boston, Mass.); Essex, M.; Rich, M. A.; Hardy, Jr., W. D. *Int. J. Cancer* 15(2):351-365; 1975.

Immune responses were studied during spontaneous regression of Friend virus (FV)-induced leukemia in CD-1 mice. Spleen enlargement of infected mice was maximal in three weeks, regression becoming distinct in four weeks in 20-40% of the animals. Regression was accompanied by loss from the spleen cells of specific FV-induced cell membrane antigen (FVMA), as determined by indirect immunofluorescence, and of virus group-specific antigens (gsa), similarly determined. The percentages of B and T cells in the spleen, determined by direct immunofluorescence, were markedly decreased during leukemia progression, but there was a subsequent increase during regression. The appearance of gsa-positive cells in peripheral blood correlated well with the early progressive and regressive phase of leukemia, up to seven weeks after infection. Later, the presence of these cells became unpredictable with respect to the status of the disease. Gsa-positive cells reappeared in the blood of most mice with regressed splenic tumors, suggesting the persistance of the virus complex in the animals. Antibody responsiveness, as determined by the numbers of hemolytic plaque-forming cells (PFC) after a single immunization with SRBC, was suppressed in leukemia progression and spontaneously recovered during regression of leukemia. However, the PFC elicited by the SRBC in both progressors and regressors expressed the specific virus-induced membrane antigen, FVMA, as demonstrated by inhibition of the PFC test with FVMA-specific antiserum and complement. The recovery of immunological responsiveness also included the spontaneous appearance of virus-neutralizing antibody to FV. However, this was not paralleled by the appearance of antibody of FVMA. Traces of anti-FVMA antibody were occasionally detectable in serum of both progressors and regressors and did not correlate with virus neutralization. This may explain the observed susceptibility of regressors to secondary relapse and to infection. It is suggested that the general improvement of immune responsiveness during regression would point to this phase of the disease as a crucial stage for active immunotherapy.

2688 T ANTIGEN BINDS TO SIMIAN VIRUS 40 DNA AT THE ORIGIN OF REPLICATION. (Eng.) Reed, S. I. (Stanford Univ. Sch. Med., Calif.); Ferguson, J.; Davis, R. W.; Stark, G. R. *Proc. Natl. Acad. Sci. USA* 72(4):1605-1609; 1975.

A technique employing ferritin-conjugated antibody was developed to visualize specific protein-dependent DNA complexes, and was employed in demonstrating the preferential location of binding of SV40 T antigen to SV40 DNA. SV40 DNA in the form of covalently closed supercoiled circles was obtained from line Ma-134 African green monkey kidney cells infected with strain WT-830 of the virus. T antigen was obtained in partially-purified form from SV40-infected CV-1 or C13/SV28 lines of cells. Anti-T sera were prepared by immunizing hamsters with purified T antigen. After serial incubation of the SV40 DNA with T antigen, anti-T γ-globulin, and ferritin-conjugated anti-hamster γ-globulin, followed by cleavage of the circular DNA to linear form by treatment with *Eco*RI endonuclease, electron dense ferritin cores could be seen bound to DNA. To be able to map the position of these bound cores, a marker for orientation, namely, *E. coli* DNA unwinding protein, for which SV40 has an affinity at specific sites, was added. Purified *E. coli* DNA unwinding protein incubated with SV40 DNA and fixed with glutaraldehyde, followed by cleavage with *Hemophilus parainfluenzae* restriction endonuclease II, permitted assignment of two preferred sites for the unwinding protein at 0.46 and 0.90 fractional length relative to the *Eco* endonuclease cleavage site. Ferritin binding mediated by T antigen could then be mapped at 0.65 and 0.70 fractional length from the *Eco*RI cleavage site. The affinity of SV40 DNA for DNA unwinding protein thus served to demonstrate the preferential binding of SV40 T antigen at or near the origin of replication of SV40 DNA, namely, 0.67 fractional length clockwise from the *Eco*RI cleavage site.

2689 SPECIFIC DEPRESSION OF THE ANTITUMOR CELLULAR IMMUNE RESPONSE WITH AUTOLOGOUS TUMOR HOMOGENATE. (Eng.) Paranjpe, M. S. (Natl. Cancer Inst., Bethesda, Md.); Boone, C. W. *Cancer Res.* 35(5):1205-1209; 1975.

The source and characteristics of the factor responsible for the specific depression (eclipse) of antitumor cellular immune response were investigated in simian virus 40 (SV40)-transformed tumor murine host system of BALB/c AnN mice. A group of E_4 (a cell line started from an explant of solid fibrosarcoma in a BALB/c mouse produced by inoculating it with SV40-transformed BALB 3T3 cells) tumor-immune mice received, ip, 0.25 g of homogenized homologous tumor. The mice were challenged 24 hr later with 10^6 E_4 tumor cells, and the cell-mediated immune response was measured *in vitro* by radioisotopic (^{51}Cr) footpad assay. Treated mice gave a lower foot count ratio than untreated E_4-immune mice (1.22 versus 2.83, respectively). No depression of foot count ratio was observed with an ip inoculate of an equal amount of homogenate from an antigenically unrelated syngeneic methylcholanthrene-induced tumor. Inoculation of the tumor homogenate to tuberculin-sensitized mice did not alter their footpad reactivity to tuberculin. The fraction of tumor homogenate that suppressed antitumor response of immune mice could be extracted by 3 M KCl. The authors conclude that the ip inoculation of E_4 tumor homogenate does not cause general immunosuppression, but rather produces specific eclipse of the antitumor cellular immune response.

2690 DIFFERENTIAL INDUCTION OF TUMOUR ANTIGENS BY TRANSFORMATION-DEFECTIVE VIRUS MUTANTS. (Eng.) Kurth, R. (Dept. Tumour Virology, Imperial Cancer Res. Fund Lab., P.O. Box 123, Lincoln's Inn Fields, London, WC2A 3PX, England). *J. Gen. Virol.* 28(2):167-177; 1975.

Normal rat kidney cells infected by a variety of transformation-defective temperature-sensitive avian leukosis sarcoma virus mutants were tested for the expression of transformation characteristics at permissive and restrictive temperature. Morphology, growth behavior and agglutinability by concanavalin A corresponded fully to the phenotype of the infected cells; at permissive temperature the cells resembled wild type virus transformed cells, whereas when grown under restrictive conditions they became virtually indistinguishable from normal cells. The quantitative expression of allo- or xenogeneic cell surface antigens was not significantly affected by the phenotype of the cells. Two out of the five tested mutants induced tumor antigens in the expected temperature-dependent manner, whereas the other three mutants were able to induce tumor-specific cell surface antigens even in the revertant cells cultured at the restrictive temperature. These findings extend previous results about tumor antigen induction in mutant-infected cells of the natural host, the chicken embryo fibroblasts. There may be value in the transformation-defective tumor antigen-positive mutants for vaccination purposes.

2691 REACTIVITY TO TUMOUR-ASSOCIATED ANTIGENS DETECTED IN MICE UNDERGOING LIVER REGENERATION. (Eng.) Hellstrom, I. (Univ. Washington Med. Sch., Seattle); Hellstrom, K. E.; Nishioka, M. *Nature* 253(5494):744-746; 1975.

The reactivity of lymph node cells (LNC) from mice undergoing liver regeneration to tumor-associated antigens was investigated. Partial hepatectomy was performed on BALB/c and C3H mice, removing 65-75% of the hepatic parenchyma; littermates underwent sham-hepatectomy. Mice were bled from the retro-orbital sinus; sera were stored for testing of blocking activity; and the animals were killed and tested for LNC-mediated reactivity. A BALB/c methylcholanthrene-induced sarcoma line, a BALB/c Moloney sarcoma virus-transformed 3T3 line, BALB/c fibroblasts from newborn mice, and nontransformed BALB/c 3T3 cells were used as targets in microcytotoxicity assays. LNC from hepatectomized mice were found to be cytotoxic to the two tumor lines used as targets, as compared to LNC from sham-hepatectomized mice. However, no consistent cytotoxic effect against the untransformed, control cells was observed. The data indicated that sera from the hepatectomized mice could abrogate the cytotoxic effect of LNC from multiparous and hepatectomized mice, as compared with sera from sham-operated controls. The specificity demonstrated suggests that an immune reaction to some antigens present on tumor cells and regenerating liver cells is responsible for these findings, rather than a more nonspecific destruction of tumor cells. It is further suggested that a normal tissue repair process, involving rapid cell division, may lead to a detectable immunological reaction against antigen present on neoplastic cells.

2692 A FETUIN-LIKE ANTIGEN FROM HUMAN NEPHROBLASTOMA. (Eng.) Wise, K. S. (Sch. Dentistry, Univ. Southern California, Los Angeles, Calif. 90007); Allerton, S. E.; Trump, G.; Powars, D.; Beierle, J. W. *Int. J. Cancer* 16(2):199-210; 1975.

The characterization of an antigen in human nephroblastomas is presented. The antigen was detected in pooled tumor suspensions using antiserum prepared in rabbits against an EDTA extract of the tumors. This antigen was not found in normal human plasma or kidney extracts, and was not related to the ABO or Forssman blood groups. The antigen was detected in extracts of cultured nephroblastoma cells, but was not present in extracts of normal human fetal kidney cell cultures. It is believed to be present at the cell surface, as cell viability was not significantly lowered during the extraction procedure. A reaction of complete identity was demonstrated by Ouchterlony double diffusion experiments with this antigen and purified bovine fetuin. The antigen was not detected in extracts of human fetal spleen, thymus or kidney, nor in human fetal serum. Furthermore, it does not possess determinants in common with the human alpha-fetoprotein of hepatomas, nor was it detected in human renal clear cell carcinoma. Initial characterization of the antigen showed it to be nondialysable, not sedimentable at 100,000 x g for two hours, stable to repeated freeze-thawing and to

incubation at 56 C for one hour, and water soluble over a wide pH range. The antigen was susceptible to digestion with pronase and trypsin and possibly hyaluronidase, but not to ribonuclease or neuraminidase. The protein portion is therefore of major importance to the structural integrity of this antigen. The relationship between this antigen and other abnormal materials reported previously in nephroblastoma patients is being studied.

2693 SHARED IDIOTYPIC DETERMINANTS ON B AND T LYMPHOCYTES REACTIVE AGAINST THE SAME ANTIGENIC DETERMINANTS: III. PHYSICAL FRACTIONATION OF SPECIFIC IMMUNOCOMPETENT T LYMPHOCYTES BY AFFINITY CHROMATOGRAPHY USING ANTI-IDIOTYPIC ANTIBODIES. (Eng.) Binz, H. (Dept. Immunology, Uppsala Univ., Uppsala, Sweden); Wigzell, H. *J. Exp. Med.* 142(5):1231-1240; 1975.

Normal T lymphocytes from Lewis rats were incubated with an anti-(Lewis-anti-BN) antiserum. This caused subsequent selective retention of potential graft-*vs*-host (GvH)-reactive cells against BN on anti-Ig columns, whereas Lewis T cells with reactivity against DA or August (Au) (carrying distinct Ag-B antigens in comparison to BN) passed through. The retained cells could be eluted, and were shown to display highly increased reactivity against BN with virtually no reactivity left against DA or Au antigens. Analogous results were obtained using an anti-(Lewis-anti-DA) antiserum. Using chromatography and anti-Ig columns selectively enriched or deleted T lymphocytes were analyzed for the presence of idiotypic cells as well as specific GvH reactivity. A highly significant positive correlation was found between the percentage of a given idiotype in a population of T cells and the relevant GvH potential of the same population. Because of this, it is apparent that the idiotype-positive T cells that can be visualized are the very same T cells that express immune reactivity against the expected antigens. The data thus directly demonstrates the existence of a largely nonoverlapping population of immunocompetent T cells capable of reacting against the various *Ag-B* locus antigens in the rat. Highly purified, functionally intact immunocompetent T lymphocytes with restricted immune reactivity can thus be produced from normal lymphocyte populations for further analysis.

2694 B AND T CELLS IN A CAT WITH THYMIC LYMPHOSARCOMA. (Eng.) Mackey, L. (Leukaemia Res. Unit, Univ. Glasgow, Bearsden, Glasgow G61 1OH, Scotland); Jarrett, W.; Jarrett, O.; Wilson, L. *J. Natl. Cancer Inst.* 54(6):1483-1487; 1975.

The mixed antiglobulin reaction and guinea pig RBC test were applied to malignant and normal cells from a cat with thymic lymphosarcoma, where the two cell populations were morphologically distinct. The cells reacting in these tests (B and T cells) formed separate, nonoverlapping populations. The malignant cells were large lymphoblasts replacing the normal thymus and infiltrating local lymph nodes, where they localized only in the paracortical, i.e., thymus-dependent areas. Cells from the nodes could therefore be identified as malignant or normal by their size. The mixed antiglobulin reaction showed that the malignant cells did not carry the surface Ig characteristic of B cells, whereas these malignant cells formed nonimmune rosettes with guinea-pig RBC. Among lymph node cells, most surviving normal small lymphocytes, from outside the thymus-dependent areas, reacted as B cells. The morphologic evidence therefore corroborated the test results, which indicated that the formation of rosettes with guinea-pig RBC seems a reliable means for the demonstration of T cells in the cat.

2695 IDENTIFICATION OF LYMPHOID CELLS IN CULTURES OF MURINE LEUKOCYTES AND THYMUS. (Eng.) Burke, T. R. (Springville Lab., N.Y.); Moore, G. E.; Stobo, J. D. *Cancer Res.* 35(3):673-678; 1975.

Several culture conditions and media were studied in an effort to establish long-term cultures of murine lymphoid cells from blood and thymus. Mouse strains C3H/St Ha MF+, C57BL/6Ha, and DBA/I were used for a source of thymus cells, while WBC were obtained from C3Hf /HeHa mice. Media including RPMI 1640, 1700, 1701, 1715, GEM1717, NCTC, fetal calf serum (FCS) and horse-serum supplements, and conditioned medium. Cells in the third passage were harvested for chromosomal analysis, and subcultures from thymus cell lines and cultured lymphoid cells were used in studies of mitogen reactivity in mixed lymphocyte cultures, respectively. The probability of thymus cell line-initiation seemed highest when thymuses from 1-mo-old mice were cultured with GEM 1717 medium supplemented with 20% heat-inactivated FCS. Use of supplemented RPMI medium yielded the longest survival times for WBC cultures, generally a few months. Light microscopy of thymus cells revealed many small, round to ovoid cells possessing small, dark, round nuclei which were apparently lymphoid; other pleomorphically shaped cells were also present, with a preponderant epithelioid cell type noted in a late passage. All chromosomes seen were normal acrocentrics of 2*n* karyograms, with an abundance of binucleated cells. A fluorescence antibody assay of cultured thymic theta lymphoid cells revealed that they were negative for surface immunoglobulin and θ antigen. Mitogen reactivity indicated that subculture cells were capable of reacting to phytohemagglutin and concanavalin A by initiating DNA synthesis, and that there was a nondifferential response to the classical T-dependent mitogens. One-way MCL results indicated low but positive mixed lymphocyte reactivity function by the long-term cultured lymphoid cells. It is suggested that the cells represent a class of T cells that have all but lost θ antigen, possibly due to prolonged passage.

2696 *IN VIVO* STUDIES OF DIFFERENTIATION OF THYMUS-DERIVED LEUKEMIC CELLS. (Eng.) Barker, A. D. (Battelle's Columbus Lab., Ohio); Waksal, S. D. *Ann. N.Y. Acad. Sci.* 249:484-491; 1975.

Changes in differentiation patterns in neoplastic

thymus-derived lymphocytes (T-cells) subpopulations following second and third *in vivo* passage were investigated. The behavior of leukemic T-cell subpopulations in splenectomized and thymectomized preleukemic mice was also studied. In the original experiments, transplantation of 10^5 LTC_1, LSC_1, or $LLNC_1$ from AKR mice with spontaneous leukemia into preleukemic AKR mice resulted in three different disease pathologies. When the lymphoid cells from these mice were repassaged into preleukemic recipients, all mice exhibited the distinct disease pattern seen in animals originally implanted with $LLNC_1$. Preleukemic mice implanted with LTC_3, or $LLNC_3$ also displayed enlargement of lymphoid tissues reminiscent of mice given $LLNC_1$. These three groups of mice showed the largest percentage of animals dying before the 18 day termination date, all displaying thymic atrophy, gross splenomegaly, and moderate lymph node enlargements. The three different types of disease pathologies resulted from a sequential T-cell differentiation process. Passage of LTC_1 and LSC_1 leukemic T-cells into thymectomized or splenectomized mice caused splenomegaly and lymph node enlargement. The stage of differentiation of the subpopulations was apparently related to the lymphoid compartment of origin; the number of differentiated cells in each compartment was lymph node > spleen > thymus. Thymus removal did not appear to block the differentiation process, while control of the differentiation and release of thymocytes occurred in both intact and splenectomized animals. The data suggest that leukemic T-cells exist as subpopulations in various stages of differentiation, and retain many characteristics of normal T-cells.

2697 ADULT THYMECTOMY RESULTS IN LOSS OF T-DEPENDENT MITOGEN RESPONSE IN MOUSE SPLEEN CELLS. (Eng.) Jacobs, D. M. (Dep. Biol., Univ. California, San Diego); Byrd, W. *Nature* 255(5504): 153-155; 1975.

Responses to phytohemagglutinin (PHA, 2.5 μg/ml) and concanavalin A (Con A, 10 μg/ml) were investigated in adult thymectomized mice to determine if responsiveness to these mitogens could be attributed to subpopulations of T cells. Female BDF_1 (C57-BL/6 female x DBA/2 male) mice were subjected to complete thymectomy or sham thymectomy at four weeks of age. Spleen cells obtained from mice (aged 8-20 wk) were cultured with the mitogens, and the cultures were pulsed with 50 μl of ^{125}I-5-iodo-2-deoxyuridine (1 μCi/ml). The cells were then counted in an automated gamma-counter. The results show that adult thymectomy initially caused an increase in the response of spleen cells to PHA and Con A. This was followed by a rapid and sustained decay of responsiveness to the same mitogens, whereas cells from sham-thymectomized mice continued to increase to their mature adult level of responsiveness to the two mitogens. This divergence of responsiveness between thymectomized and normal mice was not observed with a thymus-independent B-cell mitogen, lipopolysaccharide (20 μg/ml). The decay in responsiveness to PHA and Con A is consistent with the existence of two populations of T cells: one required for the bulk of mitogen response which decays completely by nine weeks after thymectomy, and the other a long-lived population that responds poorly to PHA and Con A.

2698 STIMULATION IN THE MIXED LEUKOCYTE CULTURE AND GENERATION OF EFFECTOR CELLS IN CELL MEDIATED LYMPHOLYSIS BY A HUMAN T LYMPHOBLAST CELL LINE. (Eng.) Callewaert, D. M. (Wayne State Univ. Sch. Medicine, 540 E. Canfield, Detroit, Mich. 48201); Kaplan, J.; Peterson, W. D.; Jr.; Lightbody, J. J. *Cell Immunol.* 19(2):276-281; 1975.

A lymphoblast cell line possessing B cell surface markers and a line possessing T cell surface markers, each derived from the same patient, were tested for their ability to stimulate in the mixed leukocyte culture (MLC) reaction and their ability to generate effector cells in cell-mediated lympholysis (CML). Both the T and B cell lines were capable of stimulating human peripheral blood lymphocytes in the MLC reaction; however, the T cell line required four times as many cells for an equivalent response. Generation of effector cells in CML was achieved when both the T and B cells were used as stimulator cells, but the T cell line generated a much higher degree of ^{51}Cr release. These results are in agreement with a previous report indicating that human B cells possess strong stimulating capacity while T cells possess weak but significant MLC stimulating activity.

2699 REACTIVITY OF ANTIHUMAN THYMOCYTE WITH ACUTE LEUKEMIC BLASTS. (Eng.) Mills, B. (Milwaukee Children's Hosp., 1700 West Wisconsin Ave., Milwaukee, Wis. 53233); Sen, L.; Borella*, L. *J. Immunol.* 115(4):1038-1044; 1975.

Normal and leukemic lymphoid populations were examined to determine if the formation of spontaneous E rosettes correlated with the presence of thymus-associated cell surface antigens. Lymphoblasts from four of 12 children with acute lymphoblastic leukemia (ALL) formed spontaneous E rosettes at 4°C and 37°C(E^+) and bound rabbit antihuman thymocyte serum, as determined by indirect immunofluorescence and by an indirect radiolabeled antibody assay. The blasts from the other eight children did not form E rosettes at 4 or 37°C(E^-) and did not bind antithymocyte serum. Absorption of the antiserum with peripheral blood leukocytes removed all detectable reactivity with normal peripheral blood lymphocytes, normal bone marrow cells and E^- bone marrow cells, but did not remove all reactivity with thymus cells or E^+ leukemic blasts. Absorption of the antiserum with thymus from one donor removed all reactivity against thymus cells from another donor. After absorption with normal peripheral blood leukocytes, the antithymocyte serum reacted with E^+ leukemic blasts but not with remission lymphocytes from the same patients. Thus, there are at least two distinct thymus-associated antigens-one that is present on T lymphocytes from peripheral blood as well as thymus and another that is present only on normal thymus and on ALL blasts that are identified by their ability to form E rosettes at 37°C.

2700 E RECEPTORS ON BLASTS FROM UNTREATED ACUTE LYMPHOCYTIC LEUKEMIA (ALL): COMPARISON OF TEMPERATURE DEPENDENCE OF E ROSETTES FORMED BY NORMAL AND LEUKEMIC LYMPHOID CELLS. (Eng.) Borella, L. (St. Jude Child. Res. Hosp., Memphis, Tenn.) and Sen, L. *J. Immunol.* 114(1):187-190; 1975.

The temperature sensitivity of SRBC rosettes formed by normal human lymphocytes was compared with the sensitivity of SRBC rosettes formed by the blasts of 29 untreated children with acute lymphocytic leukemia (ALL). Rosette formation by normal thymic cells, by bone marrow lymphocytes from ALL children, by blood and bone marrow lymphocytes from children in remission for a minimum of 4.5 yr were compared at 4 C and 37 C. TC199 (0.2 ml) containing 1.5 x 10^6 lymphoid cells and an equal volume of 0.5% SRBC was incubated at 37 C for five minutes, after which the suspension was centrifuged and incubated at 4 C or 37 C for one hour. The cells were resuspended, and 1,000 cells were counted to determine the percentage of rosettes. The lymphocytes of six patients formed rosettes (SRBC-positive cells). Of these patients, four had a thymic mass and all had WBC counts greater than 5 x $10^4/mm^3$. Two of 23 with SRBC-negative ALL had WBC counts greater than 5 x $10^4/mm^3$, and none of the 23 had a thymic mass. Cells from children in ALL remission formed 11% rosettes at 4 C, and 1% rosettes at 37 C. Thymus cells formed 83% rosettes at 4 C and 76% at 37 C, while SRBC-positive ALL cells formed 57% at 4 C and 48% at 37 C. Rosette formation in the lymphocytes of two children was 58% at 4 C and 38% at 37 C prior to treatment; after six days of chemotherapy (vincristine, prednisone and asparaginase) this fell to 42% at 4 C and 0% at 37 C. The results suggest rosette formation in ALL is correlated with high WBC counts and/or a thymic mass at diagnosis. ALL cells and thymic cells form rosettes at 37 C, while normal lymphocytes do not. SRBC rosette formation may serve as another parameter to evaluate the differential effects of cytotoxic agents on normal and neoplastic cells.

2701 DEPRESSION OF IN VITRO RESPONSIVENESS TO PHYTOHEMAGGLUTININ IN SPLEEN CELLS CULTURED FROM CHICKENS WITH MAREK'S DISEASE. (Eng.) Theis, G. A. (New York Medical Coll., Valhalla, N.Y. 10595); McBride, R. A.; Schierman, L. W. *J. Immunol.* 115(3):848-853; 1975.

Studies were undertaken to determine what effect Marek's disease virus (MDV) infection and oncogenesis might exert on phytohemagglutinin (PHA) responsiveness of T lymphocytes in two sublines of Marek's disease (MD)-susceptible inbred White Leghorn chickens (lines G-B1 and G-B2). Cultures of dispersed spleen cells, prepared from chickens with MD visceral lymphomas that had been given an ip injection of blood from MDV-infected chickens (0.5 ml 1:5 dilution), showed marked depression of responsiveness to PHA (2 µl/ml), as measured by tritiated thymidine (^{3}H-Tdr) incorporation in cells *in vitro*. When data were expressed quantitatively in terms of cpm/10^5 viable cells, the functional depletion of PHA-responsive cells appeared to result from lower levels of ^{3}H-Tdr incorporation in the PHA-stimulated spleen cultures from chickens with acute MD symptoms, as compared to similar cultures from uninfected isolator-reared control chickens. It is suggested that depression of PHA-induced blastogenesis in spleen cell cultures from chickens with acute MD reflects virus-related alterations in T lymphocytes.

2702 REDUCED LYMPHOCYTE TRANSFORMATION IN EARLY CANCER OF THE BREAST. (Eng.) Knight, L. A. (King's Coll. Hosp. Medical Sch., London, England); Davidson, W. M. *J. Clin. Pathol.* 28(5):372-376; 1975.

The cell-mediated immune response was measured *in vitro* by lymphocyte transformation in 53 patients with malignant breast tumors and in 53 patients operated upon for benign tumors. Both groups were of similar ages. Lymphocyte preparations from WBC-rich plasma were sedimented by gravity or slight centrifugation, placed in medium TE 199 supplemented with 20% autologous or human serum, and treated with phytohemagglutinin (PHA, 4 µg/ml), or with pokeweed mitogen (0.04 ml/ml). After the cultures were incubated at 37 C for 48 hr, tritiated thymidine (1 µCi/ml) was added, and after 68 hr incubation, Colcemid (0.6 µg/ml) was added. After reincubation for four hours, the uptake of the radioactive DNA precursor was measured in portions of the cultures by scintillation procedures, and the percentage of cells incorporating the label was determined by autoradiography. When the medium contained standard human serum, the uptake of tritiated thymidine was 26.40% by lymphocytes from patients with malignant breast cancer, and 34.63% by lymphocytes from subjects with benign tumors. The corresponding values for the percentage incorporation were 47.60% and 60.79%, respectively. The differences were statistically significant. Similar results were found when the medium contained autologous serum. Differences in the same direction were observed with the use of pokeweed mitogen, but they were not statistically significant. Reduced lymphocyte transformation was present preoperatively, and even very early in the disease. The reduction appeared to be even more marked in the advanced cases. It appears significant that plasma from these cancer patients contains a factor which reduces the PHA transformation of lymphocytes from a healthy donor, although contradictory findings have been reported by other investigators.

2703 BIOLOGICAL DIFFERENCES BETWEEN EPSTEIN-BARR VIRUS (EBV) STRAINS WITH REGARD TO LYMPHOCYTE TRANSFORMING ABILITY, SUPERINFECTION AND ANTIGEN INDUCTION. (Eng.) Menezes, J. (Ste. Justine Hosp., Montreal, P.Q., Canada); Leibold, W.; Klein, G. *Exp. Cell Res.* 92(2):478-484; 1975.

Epstein-Barr viruses (EBV) that inhibit growth of an established EBV-carrying Raji line or transform cord blood lymphocytes (CBL) were subjected to four tests in order to determine if transformation and growth inhibition are due to the same type of virus particle. Six different sources of EBV were tested for CBL transformation, early antigen induction in Raji cells, inhibition of Raji cell growth, and induction of EBV-determined nuclear antigen (EBNA) in

CBL. The EBV-producer lines used as virus donors were P3HR-1, B95-8, 833L, QIMR-WIL, F137, and cb-8-7. Lymphocytes prepared from human umbilical cord blood within 20 hr after collection were separated on a Ficoll-isopaque gradient and cultured in RPMI-HEPES buffer. Primary CBL cultures were infected with serially diluted EBV, and transformation was assessed in a microculture system with twice-weekly microscopic examination. EBV-determined antigens were detected by immunofluorescence. Growth inhibition was measured by a micromethod, the end-point being taken as the highest virus dilution that produced at least 75% inhibition in relation to uninfected controls. The B95-8 virus transformed and induced EBNA in CBL; the virus neither induced early antigen in Raji cells, nor inhibited their growth. P3HR-1 virus did not transform CBL or induce EBNA or EV in CBL, but did induce early antigen in Raji cells and inhibit their growth. EBV isolated from cell lines QIMR-WIL, 833L, F137 and cb-8-7 resembled the B95-8 virus. The findings indicate that the early antigen inducing and growth-inhibitory properties of the P3HR-1 virus, and the transforming activity of the B95-8 and other cell line viruses, are mutually exclusive viral functions.

2704 THE ROLE OF MACROPHAGES IN THE GENERATION OF T-HELPER CELLS: I. THE REQUIREMENT FOR MACROPHAGES IN HELPER CELL INDUCTION AND CHARACTERISTICS OF THE MACROPHAGE-T CELL INTERACTION. (Eng.) Erb, P. (Dept. Zoology, Univ. Coll., London, WC1E 6BT, England); Feldmann, M. *Cell Immunol.* 19(2):356-367; 1975.

The role of macrophages in the induction of helper cells *in vitro* was investigated. When either soluble or particulate antigens were used, macrophages were found to be essential. This was true regardless of the anatomical source of the T cells (spleen, lymph node or the cortisone resistant pool of the thymus), or of the method of macrophage depletion, (adherence to polystyrene or nylon wool, or by the use of carbonyl iron). There were some differences, however, depending on the physical nature of the antigen used. With soluble antigen, 2-mercaptoethanol or allogeneic macrophages would not overcome the macrophage deficit, whereas they did with particulate antigen. The nature of the interaction between macrophages and T cells was investigated using flasks with double chambers, separated by a nucleopore membrane with 0.2 μm pores. The results indicate that cell contact was not necessary; macrophages functioned normally when in either the upper or the lower compartments. Since physical contact was not required between T cells and macrophages for helper cell induction, macrophages release mediators which interact with T cells.

2705 SUSCEPTIBILITY AND RESISTANCE OF CHICKEN MACROPHAGES TO AVIAN RNA TUMOR VIRUSES. (Eng.) Gazzolo, L. (Unit Virology, I.N.S.E.R.M., Lyon, France); Moscovici, M. G.; Moscovici, C. *Virology* 67(2):553-565; 1975.

This study provides new information on the susceptibility of chicken macrophages to avian leukosis and sarcoma viruses of various subgroups. Cultures of embryonic macrophages were derived from chicken yolk sac; those of adult macrophages, from peripheral blood of chickens. Cultures of fibroblasts were derived from chick embryos. Cells for most experiments came from line 6 white Leghorn embryos, but fertile eggs of other lines and of various fibroblast phenotypes (relating to resistance to virus subgroups) were also used. Viruses studied were Rous-associated leukosis viruses, myeloblastic-associated leukosis viruses, transformation-defective B77 virus, ring-necked pheasant virus, and golden pheasant virus, together representing a variety of subgroups. Also studied were Bryan high-titer Rous sarcoma virus R(-), R(-) pseudotypes with leukosis viruses, R(-) pseudotype with chicken helper factor R(chf), Prague strain Rous sarcoma viruses, Schmidt-Ruppin Rous sarcoma viruses, and avian sarcoma virus B77, also representing a variety of subgroups. Established methods were used for assaying the different viruses. For studies involving isolation of avian sarcoma virus host range recombinants, Chf-negative C/E fibroblasts were infected with sarcoma virus PRA, PRB, PRC or B77 and, when completely transformed, they were superinfected with a leukosis virus of another envelope subgroup. The mixed harvests were plated at low multiplicities in an infectious center assay. The indicator cells in the assay were chosen to exclude the subgroup of the parental sarcoma virus, so that only those sarcoma viral infectious centers registered which released progeny belonging to the subgroup of the parental leukosis virus. Single foci produced under these conditions were recloned three times at high virus dilutions. The envelope subgroup of these recombinant clones was determined on selectively resistant chicken cells by interference tests with leukosis virus of known subgroup affiliation, and by antibody neutralization. Macrophages from several genetic lines of chickens were susceptible to avian leukosis and sarcoma viruses of subgroups B and C, but were resistant to viruses of subgroups A, D, E, F, and G, even when fibroblasts derived from the same embryos were susceptible. This suggested that the macrophage-specific resistance was epigenetic. If the fibroblasts of a chicken embryo were genetically resistant to subgroup B or C, this resistance was also maintained in macrophages. Although chicken macrophages showed active phagocytosis in cultures, they could not initiate infection by the defective Bryan high-titer strain of Rous sarcoma virus, R(-). Subgroup B and C viruses also activated the endogenous chicken helper factor when they replicated in macrophages derived from factor-positive embryos. However, compared to fibroblasts, the levels of exogenous as well as endogenous virus synthesized by macrophages were reduced. Studies with viral pseudotypes and with recombinants of viral envelope markers suggested that the avian tumor viral host range in macrophages was controlled by an envelope component of the virion. In the experiments with recombinants, several viral clones were found that showed host range characteristics of both parental viruses.

2706 A QUANTITATIVE ASSAY FOR CONCANAVALIN A- AND *RICINUS COMMUNIS* AGGLUTININ-MEDIATED AGGLUTINATIONS OF RAT ASCITES HEPATOMA CELLS. RELATIONSHIP BETWEEN CONCANAVALIN A BINDING AND CELL AGGLUTINATION. (Eng.) Kaneko, I. (Faculty of Pharmaceutical Sciences, Univ. of Tokyo, Bunkyo-ku, Tokyo, Japan); Hayatsu, H.; Ukita, T. *Biochim. Biophs. Acta* 392(1):131-140; 1975.

To help provide a means for elucidating the mechanism of agglutination of tumor cells by various lectins, a quantitative method was developed for measurement of agglutination of rat ascites hepatoma by Concanavalin A (Con A) or by agglutinin from *Ricinus communis*. The method was based on the principle that the turbidity of a cell suspension is proportional to the sum of the cross-sectional area of cells and aggregates. The ascites cells (AH 13) were obtained from Donryu rats seven days after ip inoculation of 10^6 parent cells. For measurement of the degree of binding of lectin, Con A was labeled by acetylation with ^3H acetic anhydride. The assay was carried out by suspending 1 x 10^6 AH 13 cells in 0.4 ml of phosphate-buffered saline/MEM medium (95:5) containing the agglutinin. The mixture was incubated for 90 min, dispersed by gentle pipetting, and finally measured for optical density at 600 nm. When agglutination and binding were measured simultaneously, the agglutinability was determined by measuring the turbidity, the suspension was centrifuged, and the radioactivity of ^3H agglutinin bound to the cells was then determined. As predicted by theoretical considerations, the turbidity decreased when cells were aggregated and the decrease was a function of the average number of cells in aggregates. The agglutinability of the cells showed a maximum value at certain concentrations of agglutinin. By further addition of the agglutinin, the agglutinability decreased slightly from the maximum. These phenomena were observed for both lectins tested. The binding and agglutination experiments revealed that binding to approximately 20% of the total receptors caused maximal agglutination. This suggests that the receptors responsible for the agglutination constitute only a small part of the total receptors on the surface. The assay method has a satisfactory reproducibility and a high sensitivity.

2707 IMMUNE MECHANISMS IN LEUKEMIA: EVALUATION OF IMMUNOCOMPETENT CELL POPULATIONS. (Eng.) Lukasewycz, O. A. (Sch. Med., Univ. Michigan, Ann Arbor); Martinez, D.; Murphy, W. H. *J. Immunol.* 114(5):1491-1496; 1975.

2708 PROTECTIVE TUMOR IMMUNITY INDUCED BY POTASSIUM CHLORIDE EXTRACTS OF GUINEA PIG HEPATOMAS. (Eng.) Meltzer, M. S. (Natl. Cancer Inst., Bethesda, Md. 20014); Leonard, E. J.; Hardy, A. S.; Rapp, H. J. *J. Natl. Cancer Inst.* 54(6):1349-1354; 1975.

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2713 IMMUNOLOGIC EVALUATION OF HUMAN BLADDER CANCER: *IN VITRO* STUDIES. (Eng.) Elhilali, M. M. (Univ. California Los Angeles Med. Cent.); Nayak, S. K. *Cancer* 35(2):419-431; 1975.

2714 OBSERVATIONS ON POSSIBLE AUTOIMMUNE THERAPEUTIC EFFECTS IN EXPERIMENTALLY PRODUCED RAT BLADDER TUMORS. (Eng.) Fingerhut, B. (Coll. Physicians Surg., Columbia Univ., New York, N.Y.); Veenema, R. J. *Urol. Int.* 30(4):255-265; 1975.

2715 ONCO-FOETAL CROSS REACTIVITY BETWEEN HUMAN OSTEOGENIC SARCOMA AND FOETAL PERIOSTEAL FIBROBLASTS GROWN *IN VITRO*. (Eng.) Gangal, S. G. (Biology Div., Cancer Res. Inst., Parel, Bombay 400 012, India); Agashe, S. S.; Nair, P. N. M.; Rao, R. S.; Ranadive, K. J. *Indian J. Med. Res.* 63(6):851-857; 1975.

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stationen, Aarhus, Denmark); Dombernowsky, P. *Eur. J. Cancer* 11(6):425-431; 1975.

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2721 IMMUNOLOGICAL RESPONSIVENESS AGAINST TWO PRIMARY ANTIGENS IN UNTREATED PATIENTS WITH HODGKIN'S DISEASE. (Eng.) De Gast, G. C. (Dep. Med., Univ. Groningen, Netherlands); Halie, M. R.; Nieweg, H. O. *Eur. J. Cancer* 11(4):217-224; 1975.

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2723 STUDY BY BIOASSAY OF DISPOSAL OF LIVE LYMPHOMA CELLS BY RECIPIENT IMMUNE AND CONTROL RATS [abstract]. (Eng.) McCreary, P. (Rush-Presbyt.-St. Luke's Med. Cent., Chicago, Ill.); Laing, G.; Hass, G. *Lab. Invest.* 32(3):430; 1975.

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2726 MYCOBACTERIAL ADJUVANT AND ITS CARRIER. (Eng.) Hiu, I. J. (Institut de Cancerologie et d'Immunogenetique, Hopital Paul-Brousse, 14, Avenue Paul-Vaillant-Couturier, F-94 Villejuif, France). *Experientia* 31(8):983-985; 1975.

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2728 LEUKOCYTE MIGRATION IN AGAROSE: A SPECIFIC TEST FOR CELLULAR IMMUNITY TO SOLUBLE TUMOR ANTIGENS IN PATIENTS WITH CANCER [abstract]. (Eng.) Boddie, A. W., Jr. (Div. Surg. Oncol., Univ. California Los Angeles); Urist, M. M.; Chee, D. O.; Holmes, E. C.; Morton, D. L. *Fed. Proc.* 34(3):268; 1975.

2729 CELL-MEDIATED IMMUNE RESPONSES IN PATIENTS WITH WARTS. (Eng.) Morison, W. L. (Massachusetts General Hosp., Boston, Mass. 02114). *Br. J. Dermatol.* 93(5):553-556; 1975.

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2733 PRESENCE OF IMMUNOSUPPRESSIVE AGENTS WITH VARIOUS ACTIVITIES IN EHRLICH ASCITES FLUID. (Eng.) Nitta, K. (Dept. Antibiotics, Natl. Inst. Health, Kamiosaki 2-10-35, Shinagawa-ku, Tokyo 141, Japan); Umezawa, H. *Gann* 66(4):459-460; 1975.

2734 *IN VITRO* SUPPRESSION OF IMMUNOCOMPETENT CELLS BY LYMPHOMAS FROM AGING MICE. (Eng.) Jaroslow, B. N. (Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, Ill. 60439); Suhrbier, K. M.; Fry, R. J. M.; Tyler, S. A. *J. Natl. Cancer Inst.* 54(6):1427-1432; 1975.

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2736 THE ANTITUMOUR ACTIVITY OF PHYTOHEMAG-

2737-2754)

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2751 HUMAN LYMPHOCYTE ALLOANTIGEN(S) SIMILAR TO MURINE Ir REGION-ASSOCIATED (Ia) ANTIGENS. (Eng.) Arbeit, R. D. (Immunology Branch, Natl. Cancer Inst., Bethesda, Md. 20014); Sachs, D. H.; Amos, D. B.; Dickler, H. B. *J. Immunol.* 115(4):1173-1175; 1975.

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EXPRESSION IN HUMAN SARCOMA CELLS [abstract]. (Eng.) Burk, K. H. (M. D. Anderson Hosp. Tumor Inst., Houston, Tex.); Drewinko, B.; Lichtiger, B.; Trujillo, J. M. *Am. J. Pathol.* 78(1):28a; 1975.

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2756 MEMBRANE DIFFERENCES IN PERIPHERAL BLOOD LYMPHOCYTES FROM PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND HODGKIN's DISEASE. (Eng.) Mintz, U. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel); Sachs, L. *Proc. Natl. Acad. Sci. USA* 72(6):2428-2432; 1975.

2757 SELECTIVE ADHERENCE OF IMMUNE LYMPHOCYTES, SYNTHESIZING DNA TO CORRESPONDING TARGET CELLS. (Rus.) Brondz, B. D. (N.F. Gamaleya Inst. Epidemiology and Microbiology, Inst. Biological Trial of Chemical Compounds, Moscow, U.S.S.R); Kirkin, A. F.; Epikhina, S. O. *Biull. Eksp. Biol. Med.* 53(7):68-71; 1975.

2758 TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE AND ADENOSINE DEAMINASE IN HUMAN LYMPHOBLASTOID CELL LINES. (Eng.) Coleman, M. S. (Dept. Medicine, Univ. Kentucky, Lexington, Ky. 40506); Hutton, J. J. *Exp. Cell Res.* 94(2):440-442; 1975.

2759 T-CELL ORIGIN OF ACID-PHOSPHATASE-POSITIVE LYMPHOBLASTS [letter to editor]. (Eng.) Catovsky, D. (Royal Postgraduate Medical Sch., London W12 OHS, England). *Lancet* 2(7929):327-238; 1975.

2760 CONCANAVALIN A RECEPTORS ON THE SURFACE MEMBRANE OF LYMPHOCYTES FROM PATIENTS WITH HODGKIN'S DISEASE AND OTHER MALIGNANT LYMPHOMAS. (Eng.) Ben-Bassat, H. (Heb. Univ.-Hadassah Med. Sch., Jerusalem, Israel); Goldblum, N. *Proc. Natl. Acad. Sci. USA* 72(3):1046-1049; 1975.

2761 THE RELATIVE OCCURRENCE OF MACROPHAGES IN REGRESSING AND PROGRESSING MOLONEY SARCOMAS [abstract]. (Eng.) Russell, S. W. (Scripps Clin. Res. Found., La Jolla, Calif.); Doe, W. F.; Tozier, A. *Fed. Proc.* 34(3):268; 1975.

See also:

* (Rev): 2415, 2416, 2417, 2418, 2437, 2438
* (Chem): 2475, 2482, 2490, 2505
* (Viral): 2583, 2587, 2590, 2600, 2611, 2632
* (Path): 2770, 2800, 2807, 2858
* (Epid): 2882

2762 TISSUE CULTURE STUDY OF A SACROCOCCYGEAL CHORDOMA WITH FURTHER ULTRASTRUCTURAL STUDY. (Eng.) Fu, Y. S. (Inst. Pathology, Case Western Reserve Univ., Cleveland, Ohio 44106); Pritchett, P. S.; Young, H. F. *Acta Neuropathol. (Berl.)* 32(3):225-233; 1975.

A sacrococcygeal chordoma removed from a 56-yr-old man was studied in tissue culture. Fragments from the tumor were studied both before culture and after 8 and 21 days of culture. The cells were cultured in Minimal Essential Medium containing nonessential amino acids, glutamine (4 mM), 10% fetal calf serum, and antibiotics at 37 C in 5% CO_2. *In vitro*, the cells that proliferated in the early phase were predominantly nonvacuolated stellate cells, which were later transformed into vacuolated cells. This suggests that various cell types seen *in vivo* represent variants of the same cell type at different stages of differentiation and cellular activity. The *in vitro* tumor cells also showed the origin of their vacuoles from both rough endoplasmic reticulum and Golgi membranes. The finding of amorphous and granular material and collagen fibrils in the extracellular spaces of cultured cells seems to suggest that chordoma cells have certain synthetic and secretory activities.

2763 SUBCLINICAL ELASTOFIBROMAS IN THE SCAPULAR REGION IN AN AUTOPSY SERIES. ADDITIONAL NOTES ON THE AETIOLOGY AND PATHOGENESIS OF ELASTOFIBROMA PSEUDONEOPLASM. (Eng.) Jarvi, O. H. (Dept. Pathol., Univ. Turku, Finland); Lansimies, P. H. *Acta Pathol. Microbiol. Scad.* [*A*] 83(1):87-108; 1975.

In an attempt to establish causes of subclinical elastofibromas in the scapular region, a series of post mortem cases were studied. Out of 235 cases, 39 exhibited changes identical to elastofibromas in the elastic fibers in some area of the thoracic fascia. Clinical elastofibroma occurred mostly in elderly people with a marked preponderance among women. No correlation could be found between subclinical elastofibromas and the cause of death. In addition to hypertrophy and secondary degeneration of elastic fibers, necrosis of collagenous, adipose, muscular and nervous tissue, as well as formation of clefts, cysts and bursae was found in 85% of cases presenting elastic changes. Arteries exhibited breaks in the elastic layer, while venous changes were found in 90% of the cases of elastic degeneration and 30% of the cases without degeneration. Owing to the enormous hypertrophy of the fibers in the adventitia, it was very difficult to estimate whether or not new formation of the elastic fibers also played a role in venous changes. The results of the cases reviewed support the concept that the capacity of connective tissue to produce new elastic elements under certain conditions is possible, even in adult life. Direct mechanical stress on elastic tissue may be an important cause of hypertrophy and secondary degeneration of elastic fibers, and also of diffuse increase of collagenous tissue. On the other hand, nutritional deficiency due to failing resistance of the vascular system against friction of the scapula and stretching movements of the upper extremities apparently play a main part in necrotic tissue change.

2764 MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY. (Eng.) Brekke, J. H. (214 N. Fifth Ave., Virginia, Minn. 55792); Gorlin, R. J. *J. Oral Surg.* 33(11):858-865; 1975.

A case history is presented of a white male infant with a melanotic neuroectodermal tumor of infancy, the recurrence of which was clinically evident eight wk after the original lesion had been surgically removed. The lesion was first noticed at five mo. The 3 x 2 x 1.5-cm firm tumescence of the anterior left maxilla extended 3.0 cm posteriorly from the midline. The lesion was hard in the posterosuperior regions, and was slightly compressible anteriorly and inferiorly. The lesion was removed, and the postoperative course was uncomplicated until the seventh wk, when there was a swelling in the left maxilla posterior to the original lesion. The second lesion was also excised and the diagnosis of melanotic neuroectodermal tumor was confirmed histologically. The child had an uncomplicated postoperative course, and was without evidence of recurrence in his 17th postoperative month. The rapid, aggressive growth of this tumor and its propensity for recurrence make it a particularly serious and difficult lesion to manage. The author suggests that these melanotic neuroectodermal tumor cells may be induced by normal odontoblasts. If this theory is valid, it would explain the recurrences of the tumor in the maxilla and mandible.

2765 SOME NEW OBSERVATIONS IN AN INTRACRANIAL GERMINOMA. (Eng.) Hirano, A. (Montefiore Hosp. and Medical Center, 111 East 210 St., Bronx, N.Y. 10467); Llena, J. F.; Chung, H. D. *Acta Neuropathol. (Berl.)* 32(2):103-113; 1975.

A case of an intracranial germinoma from the suprasellar region of a 9-yr-old girl was examined in the electron microscope. The tumor consisted for the most part, of both large polygonal and small lymphocyte-like elements. Annulate lamellae were common in the epithelial cells. The small blood vessels were fenestrated, and the endothelial cells contained tubular bodies, membrane-bounded vacuoles containing dense fluid and occasional tubules, arrays of tubules within the nuclear envelope and rough endoplasmic reticulum, and a markedly irregular luminal surface. Dense, lamellated structure were present in the widened, collagen-containing perivascular spaces. The high frequency of annulate lamellae within the large polygonal cell components (which have previously been confirmed to be normal components of oocytes) supports the conclusion that intracranial germinomas are probably unrelated to the pineal gland and are, instead, identical to germinomas of the ovary.

2766 FINE STRUCTURE OF INTERCELLULAR JUNCTIONS AND BLOOD VESSELS IN MEDULLOBLASTOMAS. (Eng.) Hassoun, J. (Laboratoire de Neuropathologie, Faculte de Medecine. Bd. Jean-Moulin,

F-Marseille 13885, France); Hirano, A.; Zimmerman, H. M. *Acta Neuropathol. (Berl.)* 33(1):67-78; 1975.

Specimens from six cerebellar medulloblastomas (all in children) were studied by light and electron microscopy. The specimens for light microscopy were fixed in formaldehyde; for electron microscopy they were fixed in glutaraldehyde with phosphate buffer. Specimens were postfixed in osmium tetroxide, dehydrated in ethanol, and embedded in Epon or Araldite. Thin sections were stained with uranyl acetate and lead citrate. The six tumors all displayed the usual undifferentiated pattern generally associated with medulloblastoma. Two features were found which are suggested to be constant and essential characteristics of medulloblastoma. First, cell junctions were abundant between tumor cells; these were mostly desmosome-like but other closer junctions were also seen. Second, the capillary endothelia contained frequent tubular bodies and other inclusions which may be related to them. The function of the tubular bodies is unknown, but their occurrence in brain tumors is emphasized because tubular bodies are normally present in brain capillaries only in much more limited numbers.

2767 ELECTRON MICROSCOPIC AND ELECTRON HISTOCHEMICAL STUDIES ON EMBRYONAL RHABDOMYOSARCOMA OF THE ORBIT. (Eng.) Amemiya, T. (Dept. Ophthalmology, Kyoto Univ., Sakyo-ku, Kyoto-shi, Japan); Tsuboi, M.; Uchida, S. *Z. Krebsforsch.* 83(4):305-314; 1975.

Two case reports of embryonal rhabdomyosarcoma of the orbit are presented, and the results of electron microscopic and electron histochemical studies of the tumor are described. The tumors were removed from a 9-yr-old Japanese boy and a 5-yr-old Japanese boy. A small number of differentiated tumor cells were found along with a great number of undifferentiated ones in both tumors. Abnormal dense granules were found in the nuclei of undifferentiated tumor cells, but not in differentiated ones. Nonspecific filaments were seen in the cytoplasm of undifferentiated tumor cells. Differentiated tumor cells demonstrated various stages of myofibillar structures such as A, I, and Z bands, many glycogen granules, mitochondria and a basement membrane. Polyglucose particles synthesized from glucose-1-phosphate by phosphorylase activity were located in the cytoplasmic matrix of undifferentiated and differentiated tumor cells and in the karyolymph of undifferentiated tumor cells only. Polyglucose particles increased in number according to the degree of differentiation of tumor cells. These results suggest that the intranuclear dense granules found only in the undifferentiated tumor cells are glycogen granules or some products in cell division, but not destructive products.

2768 INTRAVASCULAR ANGIOMATOSIS: DEVELOPMENT AND DISTINCTION FROM ANGIOSARCOMA. (Eng.) Salyer, W. R. (Johns Hopkins Hosp., Baltimore, Md. 21205); Salyer, D. C. *Cancer* 36(3):995-1001; 1975.

Two hundred and seventy-five arterial thromboemboli and 140 venous thrombi were compared with 12 angiosarcomas in order to study the development of the angiosarcoma-like pattern in organizing thrombi and to note certain features that aid in their histologic differentiation from angiosarcoma. Three-fourths of the venous thrombi were in hemorrhoidal vessels; the remainder, and the arterial thromboemboli, were taken from autopsy and other surgical cases. Features similar to those present in angiosarcomas were found in organizing thrombi. Within the thrombi, freely anastomosing small channels, often lined by one or more layers of prominent, occasionally atypical, endothelial cells were noted. Papillary-like projections of organizing thrombus material lined by similar cells heightened the similarity of the process to angiosarcomas. The papillary-like structures appeared to develop due to a combination of endothelialization of thrombus fragments and of ingrowth of interlacing vessels. The peculiar process of thrombus organization, which has been called "intravascular angiomatosis," may be mistaken for true angiosarcoma and thus lead to unnecessary irradiation or radical surgery. The pseudoangiosarcoma differs from angiosarcoma in its confinement entirely within large vascular lumens and in its lack of mitoses, necrosis, and true solid cellular areas devoid of vascular differentiation.

2769 STRUCTURAL AND FUNCTIONAL CHARACTERISTICS OF THE MICROCIRCULATION IN NEOPLASMS. (Eng.) Papadimitriou, J. M. (Dept. Pathology, Univ. Western Australia, Perth, Western Australia); Woods, A. E. *J. Pathol.* 116(2):65-72; 1975.

The microcirculation in a transplantable rat fibrosarcoma was investigated. Methylcholanthrene-induced fibrosarcoma suspension was injected sc into neonatal Wistar rats. Venograms were performed by injecting the large veins overlying the neoplasm, and arteriograms involved intracardiac puncture. Normal and neoplastic tissues were observed by electron microscopy. Permeability studies were carried out by injecting a 2.5% trypan blue solution (iv, 25 mg/100 g) into the dermis and into the neoplasm. Histamine (0.01 mg at each injection site) was then administered, and the amount of exuded trypan blue was estimated after 30 min. The vasculature of the neoplasm consisted of irregular channels lined by plump endothelium that displayed mainly pentalaminar junctions, although a few heptalaminar junctions were also found. Few pericytes surround the endothelial layer, while the basement-membrane varied in thickness and was often duplicated and triplicated. Challenge with histamine resulted in increased permeability in comparison with normal connective tissues similarly treated. The increased permeability was accompanied by the formation of interendothelial gaps in these irregular vascular channels. Carrageenan (0.2 ml of 1% solution, sc) induced a leukocytic exudate in the neoplasm which, apart from an increase in the mononuclear concentration two weeks after injection, varied little from normal connective tissues. It is concluded that the majority of vascular channels in this neoplasm bear some structural and functional relationship to small venules.

2770 INDUCTION OF METASTASIZING CARCINOMA IN RATS AND THEIR BIOLOGICAL CHARACTERISTICS. (Eng.) Harada, Y. (Shionogi Res. Lab., 2-47 Sagisu-Kami, Fukushima-ku, Osaka, Japan). *Acta Pathol. Jpn.* 25(4):451-461; 1975.

Induction of a spontaneously metastasizing carcinoma in rats was attempted. Four-wk-old Sprague-Dawley female rats were thymectomized and/or splenectomized and fed 200 mg (20 mg x 10) of 3-methylcholanthrene from seven wk of age twice weekly for five wk. The early-appearing tumors were excised in order to select by isoimmunity the late-appearing ones that were less antigenic. The latter were easily transplanted into normal syngeneic female rats with metastasis to remote organs. This metastasizing capacity became an inherent character in syngeneic normal rats from generation to generation of transplantation. With one of these tumors (MRMT-1) many cancer cells were histologically detected in circulating blood three days after tumor transplantation and were arrested in the capillary beds of lungs. The spontaneous metastasis to lymph nodes and lungs was macroscopically found within several weeks after tumor transplantation. It is concluded that the MRMT-1 carcinoma is useful as a model for study of the mechanism of cancer metastasis, and might be applied as a screening tool for anticancer drugs that affect the initial phase of metastasis after excision of the primary tumor.

2771 DISTRIBUTION OF ELECTROPHORETIC MOBILITIES OF MOUSE THYMOCYTE SUBPOPULATIONS IN THE PRESENCE OF TUMOUR CELLS. (Eng.) Jenkins, R. (Bristol Royal Infirmary, Horfield Road, Bristol BS2 8ED England). *Immunology* 29(5):893-902; 1975.

Analysis of the electrophoretic mobility of mouse thymus cells showed two main populations, with mean mobility values of $0{\cdot}77 \pm 0{\cdot}023$ μm sec^{-1} V^{-1}cm and $0{\cdot}99 \pm 0{\cdot}015$ μm $sec^{-1}V^{-1}$cm; these absolute values varied slightly from one strain to another. Implantation of tumor cells caused the relative proportions of these two populations to change dramatically within 48 hr, when an increase in the fast-moving 'immunocompetent' thymocytes was observed. The ratio of slow to fast cells changed from 9:1 in the normal BALB/c mouse to 2:1 in the presence of the tumor cells, and this 2:1 ratio persisted throughout the remainder of the animal's life. However, inoculation of histocompatible spleen cells from a normal individual evoked only a brief response in the host's thymus. This change in ratio of slow to fast cells in the thymus is interpreted as an increased production of immunocompetent cells in response to the presence of the tumor cells.

2772 STUDIES OF A CELL LINE DERIVED FROM A HUMAN MALIGNANT MELANOMA. (Eng.) Chen, T. R. (Graduate Sch. Biomedical Sciences, Univ. Texas at Houston, Houston, Tex. 77025); Shaw, M. W. *In Vitro* 10(3/4):216-224; 1974.

Employing an *in vitro* method and new staining techniques, changes in karyotype of a heteroploid tumor cell line derived from a pulmonary metastasis of a malignant melanoma were studied over ten months of continuous cultivation. A tissue specimen was obtained from a 69-yr-old man who had been diagnosed as having a metastatic melanoma of the lung. The following chromosome staining procedures were used in most instances: (a) acid-saline-Giemsa G-banding (3-hr incubation in a saline solution containing 0.6 M NaCl and 0.06 M sodium citrate adjusted to pH 7); (b) trypsin G-banding; (c) Q-banding; and (d) C-banding using the Q--C procedure. The modal karyotype of tumor cells in a 3-wk-old culture was composed of 41 intact and 11 marker chromosomes. These markers contained three paired (disomic) and five other (monosomic) elements. The derivative cell populations in 5- to 10-mo-old cultures showed changes merely in the paired markers from disomy to monosomy, by loss of one element or by formation of a new marker chromosome. Prolonged treatment in a defined medium completely devoid of serum resulted in a selection of heteroploid cells and suppression of diploid fibroblasts. The heteroploid cultures were further enriched by collecting freely suspended cells. Growth of tumor and normal cells in mixed culture had no apparent influence on either cell type.

2773 A HUMAN/MOUSE HYBRID MODEL FOR THE STUDY OF HUMAN GENETIC FACTORS INFLUENCING TUMOR CELL GROWTH. (Eng.) Koshman, R. W. (Dept. of Surgery and Surgical-Medical Res. Inst., Univ. of Alberta, Edmonton, Alberta, Canada); Koo, J.; Thurston, O. G. *J. Surg. Oncol.* 7(4):323-327; 1975.

Somatic cell hybridization (fusion) was carried out between cells of the murine lymphoma L-5178Y(r) and a human/mouse hybrid cell model. The L-5178Y(r) line is deficient in hypoxanthine-guanine phosphorybosyl transferase (HGPRT). Using a selective medium system, it was possible to isolate hybrid cell clones having the complete complement of murine chromosomes as well as the human X chromosome on which the gene for HGPRT is located. This model system may be used to study the effect of the human X chromosome on the phenotype of the murine lymphoma. It is possible that the effect of X-linked genes on behavior of the tumor *in vivo* can be studied.

2774 HIGHLY MALIGNANT CELLS WITH NORMAL KARYOTYPE IN G-BANDING. (Eng.) Mitelman, F. (University Hosp., S-221 85 Lund, Sweden); Levan, G.; Brandt, L. *Hereditas* 80(2): 291-293; 1975.

The Giemsa banding pattern of diploid tumor cells was studied during the transformation of Ph^1-negative chronic myeloid leukemia (CML) into acute leukemia, and during the progression of Rous sarcoma virus (RSV)-induced sarcomas in rats. Initial chromosome analysis of a bone marrow preparation from a 72-yr-old man with CML showed that 100% of the metaphases had a completely normal banding pattern. All 50 cells counted after blastic transformation had the normal chromosome 2n = 46 and the 21 cells karyotyped in detail all displayed a normal Giemsa banding karyotype. Five sarcomas

induced by RSV in inbred W/Fu rats were transplanted to syngeneic rats; each tumor had a normal diploid stem line. A total of 42 cells from the five transplanted tumors had the normal chromosome number 2n = 42 and a completely normal banding karyotype. These results confirm previous findings indicating that neither the transformation of a premalignant to a malignant condition nor the progression of advanced tumors is necessarily associated with visible chromosomal alterations.

2775 A NEW HEMATOLOGIC SYNDROME WITH A DISTINCT KARYOTYPE: THE 5q - CHROMOSOME. (Eng.) Sokal, G. (Hematology -- U.C.L., Ave. Chapelle aux Champs 4, 1200 Brussels, Belgium); Michaux, J. L.; Van Den Berghe, H.; Cordier, A.; Rodhain, J.; Ferrant, A.; Moriau, M.; De Bruyere, M.; Sonnet, J. *Blood* 46(4):519-533; 1975.

Cytogenetic findings, clinical picture, and hematologic data obtained from five patients with refractory anemia and the same abnormal bone marrow karyotype, are described. The patients (four women and one man, age 32-80 yr, all Caucasian, had a partial deletion of the long arm of the No. 5 chromosome. The hematologic syndrome was practically the same in these five cases. Examination of the blood by light and electron microscopy revealed a moderate to severe, generally macrocytic anemia with slight leukopenia but normal or elevated platelet count. The bone marrow showed a depressed erythroid series and some abnormalities of the granulocytic series with an occasional excess of myeloblasts. Most of the megakaryocytes had a nonlobulated nucleus. Of the detailed hemostatic function tests carried out in four patients, the main abnormalities were low values for adhesiveness of platelets to glass beads, as well as insufficient release and poor aggregation in the presence of adrenalin (2 μg/ml) and collagen (40 μg/ml). No consistent pattern of immunoglobulin deficiency or quantitative immunoglobulin abnormality was observed. The relationship of this newly established syndrome to other hematologic diseases is discussed. The syndrome constitutes another example of the association between a specific abnormal chromosome and a distinct hematologic disorder.

2776 GENE EXPRESSION OF FOREIGN METAPHASE CHROMOSOMES INTRODUCED INTO CULTURED MAMMALIAN CELLS? (Eng.) Sekiguchi, T. (Div. Radiobiology, Natl. Cancer Center Res. Inst., Tukiji 5-Chome, Chu-O-Ku, Tokyo 104, Japan); Sekiguchi, F.; Tachibana, T.; Yamada, T.; Yoshida, M. *Exp. Cell Res.* 94(2):327-338; 1975.

Transfer of genetic information from isolated hamster chromosomes to mouse cells is described. Metaphase chromosomes isolated from Chinese hamster diploid cells were incubated with mouse Cl.1-d cells deficient in thymidine kinase activity. Two viable colonies appeared from the treated mouse cells after culturing in selective medium (HAT: 1×10^{-4} M hypoxanthine, 4×10^{-7} M amethopterine, 1.6×10^{-5} M thymidine, and 1×10^{-4} M glycine) with a frequency of about 10^{-8}. The first colony isolated (Cl.1) failed to grow. The second colony isolated (Cl.2) grew well in HAT medium and was subcultured for more than 70 generations. Cl.2 cells possessed an elevated tetrahydrofolate dehydrogenase activity of molecular species resembling that of Chinese hamster cells as shown by disc electrophoresis. The cell line also expressed surface antigen(s) specific to hamster species, as shown by mixed hemadsorption test and immune cell electrophoresis. This latter phenotype disappeared after prolonged cultivation (59 generations) of the cells in nonselective medium. The karyotype of Cl.2 cells corresponded to that of the mouse species, and was quite different from that of hamster cells. Hamster chromosomes could not be identified in any of the cell clones by detailed analysis by the banding method (Q- and C-band). Not one revertant cell was obtained among 4.2×10^8 Cl.1-d cells in the control. The technique for direct transfer of genetic information from isolated metaphase chromosomes to cells of another species may provide a complementary method for cell hybridization for genetic mapping.

2777 CYTOGENETIC ANALYSIS OF ERYTHROLEUKAEMIA IN TWO CHILDREN: EVIDENCE OF NONMALIGNANT NATURE OF ERYTHRON. (Eng.) Inoue, S. (Child Res. Cent., Detroit, Michigan); Ravindranath, Y.; Zuelzer, W. W. *Scand. J. Haematol.* 14(2):129-139; 1975.

Sequential cytogenic and cytological studies were conducted in cases of erythroleukemia in two 5-yr-old girls. Bone marrow aspirations were used to determine the differential counts, mitotic index, and classification of mitotic figures, and for chromosome analysis. In the first case the bone marrow and blood were studied on eight occasions over a period of nine months. Initial bone marrow showed no aneuplody, except occasional tetraploid cells. Four months later the marrow consisted almost entirely of pathologic blasts, and 45 of 55 cells showed the karyotype 47, +C. This aneuploid cell line persisted as a dominant clone in all subsequent specimens. In the second case the first bone marrow test showed five of 103 cells to be G trisomic; over the next three months the percentage of such cells increased to 50%. In both cases a correlation was observed between the percentage of aneuploid cells and blasts in mitosis; an inverse correlation between peripheral normoblast count and hemoglobin level was also observed, indicating that erythropoiesis was under physiological control. The authors conclude that in the case of erythroleukemia, erythroid cells do not have inherent malignant properties. Cytogenic evidence, although indirect, adds another parameter to the differentiation of this type of erythroleukemia from other forms of DiGuglielmo's syndrome.

2778 MEGALOBLASTIC CHANGES AND CHROMOSOME ABNORMALITIES OF ERYTHROPOIETIC CELLS IN ACUTE MYELOID LEUKAEMIA. (Eng.) Brandt, L. (University Hosp., S-221 85, Lund, Sweden); Mitelman, F.; Sjogren, U. *Acta Haematol. (Basel)* 54(5):280-283; 1975.

Using a Giemsa banding technique, bone marrow chromosomes were studied in nine patients with acute myeloid leukemia (AML). The age-range of the patients

was 19-79 yr (mean 49 yr), and the age-range of 15 healthy controls was 19-82 yr (mean 49 yr). The chromosome numbers were determined in 50 metaphases from each bone marrow preparation. Four patients had 100% normal diploid cells and five had 100% abnormal cells; 28-92% of the mitoses were found in erythroid cells. The percentage of erythroblasts with megaloblastoid changes was abnormally high (range 1-18% megaloblasts), but was not increased in the cases with chromosomal abnormalities. These findings indicate that chromosomal aberrations are not prerequisites for the development of megaloblasts in AML. Furthermore, abnormalities in the DNA synthesis bringing about the megaloblastoid changes may occur without influencing karyotype.

2779 CYTOGENETIC BASIS OF ACUTE MYELOID LEUKEMIA. (Eng.) Ford, J. H. (Queen Elizabeth Hosp., Woodville, South Australia 5011); Pittman, S. M.; Singh, S.; Wass, E. J.; Vincent, P. C.; Gunz, F. W. *J. Natl. Cancer Inst.* 55(4):761-765; 1975.

The chromosomes of 12 adult patients with acute leukemia were analyzed by conventional means and by Giemsa and centromeric banding techniques. Acute myeloblastic leukemia was diagnosed in seven, acute myelomonocytic leukemia in two, and acute undifferentiated leukemia in three patients. Bone marrow was aspirated from patients when in relapse or remission, and both euploid and aneuploid cells were examined. All patients showed trisomy No. 9 and many showed additional numerical or structural changes in some or all their cells. These changes included monosomy No. 21 and/or monosomy No. 8. The proportion of trisomy No. 9 cells was 30-50% in patients in full remission, and up to 100% in patients in relapse. Thus, trisomy No. 9 might be an important marker of leukemic cells. In view of the predominance of trisomies 8 and 9 and the high incidence of monosomy No. 8 in this material, it seems possible that the two chromosomes are reciprocally involved in nondisjunctional events and that leukemogenic agents could be selecting either one or the other of the trisomic karyotypes.

2780 PROLIFERATION OF INEFFECTIVE ERYTHROPOIESIS WITH NUCLEAR ABNORMALITIES AND MEGALOBLASTOID APPEARANCE IN PRELEUKAEMIA. (Eng.) Mitrou, P. S. (Zentrum der inneren Medizin, TheodorStern-Kai 7, D-6000 Frankfurt/Main 70 West Germany); Fischer, M.; Hubner, K. *Acta Haematol. (Basel)* 54(5): 271-279; 1975.

A study was undertaken to establish whether or not marked nuclear abnormalities and erythroblasts with a megaloblastoid appearance are the result of a defined disturbance of erythropoietic cell proliferation in preleukemic states. Bone marrow suspensions obtained from two patients in the early stage of acute leukemia and from two patients with refractory anemia and hypercellular bone marrow were labeled with tritiated thymidine and erythropoiesis was studied using cytophotometry and autoradiography. Megaloblastoid erythroblasts showed a decreased proliferative activity in comparison to morphologically normal cells and were in the maturation stage of E_4 (early polychromatic normoblasts) mainly in the G_1-phase. They were therefore largely comparable to the megaloblastoid erythroblasts in erythroleukemia. Erythroblasts in preleukemia with nuclear abnormalities occurred in a high percentage in the G_2-phase, or were unlabeled with a DNA content of between diploid and tetraploid value. They showed a similar proliferative behavior to megaloblasts in pernicious anemia. Early polychromatic erythroblasts arrested in G_2-phase could differentiate without mitosis into tetraploid mature erythroblasts (E_5). They could divide elsewhere endomitotically, produce binucleated E_5, or take up the DNA synthesis and become polyploid. E_4 with nuclear abnormalities did not proliferate and were mainly found in the premitotic phase.

2781 NODULAR LYMPHOMA: BONE MARROW AND BLOOD MANIFESTATIONS. (Eng.) McKenna, R. W. (Box 198 Mayo, Univ. Minnesota Hosp., Minneapolis, Minn. 55455); Bloomfield, C. D.; Brunning, R. D. *Cancer* 36(2):428-440; 1975.

Morphological and clinical features of 39 patients with nodular lymphoma were studied with particular reference to bone marrow and blood involvement. To detect bone marrow involvement, trephine biopsies followed by aspiration biopsies were performed on the posterior superior iliac spines of all patients. The degree of blood involvement was graded on the basis of the number of lymphoma cells and the degree of WBC count elevation. Twenty-one patients (54%) had bone marrow involvement at the time of initial diagnosis. Thirteen (33%) also had some degree of peripheral blood involvement. A specific cell type, the small nodular lymphoma cell, was observed in the bone marrow smears of 19 of the 21 patients with bone marrow involvement and in the peripheral blood smears of all patients with blood involvement. When large cells predominated in the lymph node or bone marrow sections, the bone marrow smears and the imprints of the lymph node and trephine biopsy demonstrated these large cells to have morphological qualities of lymphocytes rather than histiocytes. This result may indicate that nodular histiocytic and nodular lymphocytic-histiocytic lymphomas are much less common than is generally accepted.

2782 CELL RECEPTOR STUDIES ON SEVEN CASES OF DIFFUSE HISTIOCYTIC MALIGNANT LYMPHOMA (RETICULUM CELL SARCOMA). (Eng.) Habeshaw, J. A. (Univ. Med. Sch., Edinburgh, Scotland); Stuart, A. E. *J. Clin. Pathol.* 28(4):289-297; 1975.

A study was made of the cell surface receptors in seven cases of reticulum cell sarcoma in order to determine B or T lymphoid or histiocytic origin. Electron microscopy of five of the specimens confirmed the diagnosis, confirmed common features, and showed differences in the degree of cytoplasmic differentiation. The cytoplasm generally contained large numbers of ribosomes with variable amounts of rough-surfaced endoplasmic reticulum. All cases showed abundant mitochondria and prominent nucleoli. The neoplastic cells were not conspicuously fiber-forming. Ingestion of dead cells by macrophages was

noted, but there was no indication of overt phagocytosis. Phagocytic activity was assessed functionally by the ability to ingest neutral red. A "sandwich" technique was used to detect immunoglobulin-bearing cells, and their morphology was assessed by dark ground and phase contrast microscopy. Rosette tests were conducted using washed SRBC, SRBC sensitized with IgG antibody (SRBCAIgG), and SRBC with IgM antibody and complement (SRBCAC). Wide variability in receptor patterns was found for both the cases studied and for control studies: SRBC rosettes (T cells) 15-72%; SRBCAIgG rosettes 6-43%; neutral red cells 1-60%; SRBCAC receptors 7-68%; and immunofluorescent cells (B cells) 6-39%. Of the seven cases, one case indicated a histiocytic origin. The cells were phagocytically active and expressed receptors for SRBCAIgG in culture, but lacked those for SRBC and SRBCAC. In two cases cells expressed both T and B lymph markers, indicating that either the neoplastic population is derived from a subclass of lymphoid cells bearing both markers or that the lymphocytes may acquire another marker during neoplastic transformation. These cases, and two showing a normal pattern of expression, have a lymphoid origin. Two additional cases appear to be of uncertain pathogenesis, having no detectable lymphocyte receptors and showing no evidence of phagocytic function. These results appear to confirm the view of both histiocytic and lymphoid origins for reticulum cell sarcoma.

2783 VIRUS-LIKE PARTICLES IN CYSTIC MAMMARY ADENOMA OF A SNOW LEOPARD. (Eng.)
Chandra, S. (Chicago Zoological Park, Brookfield, Ill. 60513); Laughlin*, D. C. *Cancer Res.* 35(11/Part 1):3069-3074; 1975.

A new type of intracisternal virus-like particle was observed in the giant cells of a cystic mammary adenoma of a snow leopard in captivity. Masses noted in each of the four mammary glands were surgically removed and a few pieces of tumor tissues placed in formalin. Various areas of the tumor were dissected and placed in 2.5% glutaraldehyde. The tissues were sliced in 1-mm cubes, postfixed in chrome-osmium, dehydrated in ethanol, and embedded in Epon-Araldite. Thin sections were stained with uranyl acetate and lead citrate for study with the electron microscope. Of the various cell types seen in the cystic mammary adenoma, virus-like particles were seen only in the giant cells. These cells contained many relatively small nuclei that were always quite far apart. The nuclear surface was indented and the chromatin matter was marginated. The cytoplasm contained two unusual structures, one consisting of lipoid material that appeared to be disintegrating, and the other consisting of membranous elements condensed into a large mass and enclosed by a single membrane. Elements of rough endoplasmic reticulum and mitochondria were scant. Virus-like particles, 115-125 nm in diameter, budded from the lamella of endoplasmic reticulum and were studded on their inner surface with dense granules (12 nm) giving them their unique ultrastructural morphology. More than two budding particles were never seen within a cisterna. Such particles were neither seen extracellularly nor in any other cell type. Type B and Type C particles were not seen in the tumor tissue. The fact that the intracisternal particles in the snow leopard mammary tumor have a morphological similarity with other virus-like particles during the budding process indicates that they are not secretory in nature. Because particles of such an ultrastructural morphology have not been described in any other species, they might be considered characteristic to the snow leopard.

2784 PROGNOSIS OF THE SECOND BREAST CANCER. THE ROLE OF PREVIOUS EXPOSURE TO THE FIRST PRIMARY. (Eng.) Khafagy, M. M. (Mem. Hosp. Cancer Allied Dis., New York, N.Y.); Schottenfeld, D.; Robbins, G. F. *Cancer* 35(3):596-599; 1975.

The prognosis of multiple metachronous tumors after successful treatment of the first primary tumor was investigated. Eighty-two patients with asynchronous bilateral breast cancer were evaluated; the median age for the first and second cancer was 46 and 57, respectively. The majority of the first and second breast cancers (70.0% and 74.4% respectively) were infiltrating duct carcinomas; less frequently, they were lobular, medullary, colloid, and papillary types. The first and second mammary cancers were of the same histologic type in 74.4%. Axillary lymph node metastases were detected in 34.1% of the patients with first breast cancer and in 40.2% with the second breast cancer; no significant difference in the incidence of axillary lymph node metastases from the second breast cancer was found in relation to the presence or absence of positive axillary lymph nodes from the first cancer. No significant difference was found when the 5-yr survival rate of 79 patients with potentially curable second breast cancer was compared with the total number of mastectomy patients. Thus, no difference in the course of the second cancer as compared with the first has been found.

2785 SEX HORMONES IN BREAST DISEASE. (Eng.)
England, P. C. (University Hosp. South Manchester, Manchester, England); Skinner, L. G.; Cottrell, K. M.; Sellwood, R. A. *Br. J. Surg.* 62(10):806-809; 1975.

Radioimmunoassay was used to measure serum concentrations of estradiol 17β and progesterone daily throughout one menstrual cycle in 32 normal women (aged 20-49 yr), 32 women with benign disease of the breast (aged 20-49 yr) and ten women with breast cancer (aged 40-49 yr). In normal women, concentrations varied with age; women in the fourth decade had mean estradiol concentrations significantly higher during the luteal phase than did women in the fifth and third decades, and the mean concentration of progesterone in women in the fifth decade was significantly lower than that in those in the third or fourth decades. Women with cysts had concentrations of estradiol 17β which were significantly higher than normal ($P < 0.01$) in both the follicular and luteal phases. In women with cancer, the concentrations of estradiol

17β and progesterone were significantly higher than normal, but the difference was very small; much larger numbers of patients need to be studied. Concentrations of estradiol 17β and progesterone in postmenopausal women were consistently very low.

2786 ULTRASTRUCTURE OF PULMONARY GRANULOMATOSIS INDUCED IN RATS BY INTRAVENOUS COMPLETE FREUND'S ADJUVANT. (Eng.) Soler, P. (Service Prof. Turiaf, Hopital Bichat, F-75877 Paris Cedex 18, France); Bernaudin, J. F.; Basset, F. *Virchows Arch.* [Pathol. Anat.] 368(1):35-50; 1975.

Following injection of complete Freund's adjuvant, changes in the rat lung were studied with the electron microscope. Twenty female Wistar rats received two iv injections, separated by a 24-hr interval, of 0.05 ml adjuvant. Two animals were killed weekly, from 3-16 wk after the second injection. Interstitial granulomas were produced; whereas on light microscopy these appeared to consist mainly of epithelioid cells, electron microscopy showed that the granulomas were largely made up of macrophages. Epithelioid cells were few in number, atypical in appearance and limited to the periphery of some granulomas. Fenestrated capillaries were also found at the edge of the granulomas. The alveolar macrophages were increased in number and size but marked cytoplasmic vacuolation and a paucity of lysosomes are consistent with a previous suggestion that the phagocytic and migratory properties of these cells are weakened or inhibited. Alterations were found in both types of alveolar epithelial cell with the appearance of intermediate cell forms.

2787 HISTOPATHOLOGICAL STUDIES ON THE TUMOURLET OF THE LUNG WITH SPECIAL REFERENCE TO THE CYTOGENESIS OF PROLIFERATING CELLS. (Eng.) Torikata, C. (Keio Univ., Sch. Medicine, Tokyo, Japan); Kawai, T.; Yakumaru, K.; Kageyama, K. *Acta Pathol. Jpn.* 25(5):539-553; 1975.

Eight foci of tumorlets (minute peripheral tumors) of the lung and one allied lesion obtained from patients at autopsy were examined by light and electron microscopy. Specimens containing tumorlet were examined with hematoxylin-eosin, periodic acid-Schiff plus alcian-blue, Mallory stain, elastica-van Gieson and silver impregnation for routine light microscopy. As specific techniques for Amine Precursor Uptake and Decarboxylation (APUD) cells, Grimelius stain, Fontana-Masson stain, masked metachromasia, and Congo-red were used. Specimens for electron microscopy were fixed in osmium tetroxide and embedded in Epon. The eight foci of tumorlets were found in seven patients (six female, all over 60). Malignant tumors were found in five cases: two carcinomas of the urinary bladder, one gastric cancer, one ovarian cancer, and a cancer of the thyroid gland associated with polycystic kidney. Two cases also showed middle lobe syndrome. An allied lesion was seen in the lung of a patient with typical middle lobe syndrome suffering from chronic glomerulonephritis. Tumorlets were discovered in the subpleural and peribronchiolar fibrous areas. Areas containing tumorlets were comparatively whitish with less anthracosis than those in other inflammatory scars. Six out of eight foci were found in the right middle lobe, one in the right upper lobe, and one in the left lower lobe. The tumorlets consisted of small clusters of epithelial cells, which were uniform and round or spindle-shaped and had hyperchromatic nuclei with very few mitoses surrounded by fibrous tissue. Proliferating cells of five foci from four tumorlets and the allied lesion showed argyrophilia but none showed argentaffinity. Three foci from two cases were examined by electron microscopy. Electron dense granules 1,200 A - 3,000 A in diameter, were found scattered in the cytoplasm. These granules were similar to those of Kultschitzky-like cells and also to those of carcinoid tumor and oat-cell carcinoma. It is suggested that the tumorlet develops more closely in undergrowth areas of the lungs than in chronic inflammatory areas, and that this type of epithelial proliferation may have a hamartomatous character.

2788 THE FINE STRUCTURE OF SO-CALLED MINUTE PULMONARY CHEMODECTOMAS. (Eng.) Kuhn, C., III. (Washington Univ. Sch. Medicine, St. Louis, Mo. 63110); Askin, F. B. *Hum. Pathol.* 6(6):681-691; 1975.

Electron microscopy was performed on several minute tumors of the type called chemodectomas, all from the lung of a 69-yr-old Negro woman. The cells had a whorling pattern with extensive interdigitating cytoplasmic processes joined by desmosomes. Except for tangles of cytoplasmic fibrils, the tumor cells had few distinctive organelles. They had no endocrine-like granules and were not associated with nerves or basement membranes. The tumors had little resemblance to paragangliomas, but displayed a puzzling similarity to meningiomas. No definite conclusions were made as to the histogenesis of these lung tumors. Viewed in the light of recent physiologic studies, they cast doubt on the presence of special chemoreceptive paraganglia in the lung.

2789 SMALL CELL EPIDERMOID CARCINOMA OF THE ESOPHAGUS: AN OAT-CELL-LIKE CARCINOMA. (Eng.) Rosen, Y. (State Univ. New York Downstate Medical Center, 450 Clarkson Ave., Brooklyn, N.Y. 11203); Moon, S.; Kim, B. *Cancer* 36(3):1042-1049; 1975.

An esophageal tumor in a 67-yr-old Puerto Rican woman is described. The tumor was found on autopsy to consist mostly of sheets of small pleomorphic anaplastic cells with markedly hyperchromatic nuclei and little cytoplasm. There were foci of squamous differentiation in the tumor and epidermoid carcinoma adjacent to it. This tumor is considered to be a small cell anaplastic variant of epidermoid carcinoma. Metastases found in the liver, bones, and lymph nodes exhibited only the anaplastic small cell appearance. Electron microscopy showed advanced

postmortem autolysis. Demonstration of intracytoplasmic neurosecretory granules is necessary for the certain identification of oat cell carcinoma. Four similar cases in the literature could not be diagnosed with certainty. The occurrence of true oat cell carcinoma of the esophagus is still in question.

2790 MUCOCELES OF THE APPENDIX: THEIR RELATIONSHIP TO HYPERPLASTIC POLYPS, MUCINOUS CYSTADENOMAS, AND CYSTADENOCARCINOMAS. (Eng.) Qizilbash, A. H. (Henderson General Hosp., 711 Concession St., Hamilton, Ontario, Canada L8V 1C3). *Arch. Pathol.* 99(10):548-555; 1975.

Sixty-four cases of hyperplastic polyp, mucinous cystadenoma, and cystadenocarcinoma of the appendix were studied in relation to the development of mucocele and "pseudomyxoma peritonei." Thirty-three cases were examples of hyperplastic polyps. In 11, the appendix was transformed into a mucocele; eight were associated with mucinous cystadenoma and one with mucinous cystadenocarcinoma. The hyperplastic polyp alone was the cause of mucocele formation in two. Thirty-five cases represented examples of mucinous cystadenoma; 32 resulted in mucocele formation. Rupture with localized pseudomyxoma peritonei was found in six; generalized pseudomyxoma peritonei was encountered only once. In four of the five cases of mucinous cystadenocarcinoma, the appendix was grossly transformed into mucoceles. The histological features of mucinous cystadenoma are identical to villous adenoma of the large bowel and probably represent its counterpart within the appendix.

2791 A REAPPRAISAL OF STAGING AND THERAPY FOR PATIENTS WITH CANCER OF THE RECTUM. I. DEVELOPMENT OF TWO NEW SYSTEMS OF STAGING. (Eng.) Feinstein, A. R. (333 Cedar St., New Haven, Conn. 06516); Schimpff, C. R.; Hull, E. W. *Arch. Intern. Med.* 135(11):1441-1453; 1975.

A taxonomy was prepared for unclassified medical data. Two new systems of staging in a cohort of 318 patients were developed and tested. The first system, which can be applied before treatment, is divided into four composite stages that contain elements of symptomatic, chronometric, co-morbid, and para-morbid data, as well as information obtained from physical examination, sigmoidoscopy, and roentgenography. The second system, applicable to patients with resected tumors, is based on a combination of pretherapeutic clinical information and postsurgical anatomic evidence. The two systems produce prognostic gradients that are clinically distinctive and statistically efficacious.

2792 FUNCTIONAL AND STRUCTURAL ALTERATIONS OF LIVER ERGASTOPLASMIC MEMBRANES DURING DL-ETHIONINE HEPATOCARCINOGENESIS. (Eng.) Gravela, E. (Istituto di Patologia generale, Universita di Torino, Corso Raffaello 30, 10125 Torino, Italy); Feo, F.; Canuto, R. A.; Garcea, R.; Gabriel, L. *Cancer Res.* 35(11/Part 1):3041-3047; 1975.

Different functional and structural properties of rat liver microsomes were studied during hepatocarcinogenesis induced by 0.25% DL-ethionine. Mal and female Wistar rats were fed a diet containing the DL-ethionine for a maximum of 5.5 mo, followed by 1-4 mo of basal diet. Microsomes were isolated from liver homogenates that had been immersed in 0.154 M sodium phosphate buffer (pH 7.4). During the first to fourth months of ethionine feeding, great decreases of cytochrome P-450 content, reduce NADP-dependent lipid peroxidation, and aminopyrine demethylase activity occurred. No changes in the reduced NADP-cytochrome *c* reductase activity were observed using spectrophotometry and by changes in the relative proportions of phospholipid fatty acids in microsomes. After the end of ethionine feeding, when hyperplastic nodules (90%) and/or hepatomas (70%) were present, the above functional and structural parameters were studied in the latte tissues, as well as in surrounding nonnodular liver. Decreases in cytochrome D-450 content, lipi peroxidation, and aminopyrine demethylase activity were documented in hyperplastic nodules and hepatomas. In hepatomas, the alterations were more marked and decrease of reduced NADP-cytochrome *c* reductase activity was also found. All these functional parameters were normal in surrounding nonnodular liver. Similarly, alterations in phospholipid fatty acid composition disappeared in surrounding nonnodular liver, but they partially persisted in both hyperplastic nodules and hepatomas. In contrast, the increase in membrane-free ribosomes also occurred in surrounding nonnodular liver, although to a lower extent than in hyperplastic nodules and hepatomas. These data are discussed in relation to the problem of the cellular precursors of hepatomas.

2793 FETAL MESENCHYMAL HAMARTOMA OF KIDNEY: A TUMOR OF SECONDARY MESENCHYME. (Eng.) Wigger, H. J. (Coll. Physicians & Surgeons, Columbia Univ., 630 West 168th St., N. Y. 10032). *Cancer* 36(3):1002-1008; 1975.

A case of fetal mesenchymal hamartoma (FMH) of the kidney is presented, and its pathologic ultrastructure is described. A 12 x 9 x 7 cm FMH was removed from a 7-wk-old infant. Grossly, the tumor tissue did not have the usual fibromyoma-like appearance, but was much more homogeneous and grayish-white in color. Histologically, the tumor consisted of poorly differentiated spindly to plump oval mesenchymal cells, irregularly arranged, with ten mitoses per high power field. Small areas of normal renal parenchyma, projections of tumor into the kidney, and absence of necrosis, hemorrhage and compression on capsule formation were also noted. By electron microscopy, the tumor cells had nuclei of variable contour, with coarsely clumped chromatin and 1-2 nucleoli. The cytoplasm contained small amounts of abnormal endoplasmic reticulum which was sometimes devoid of ribosomes. Mitochondria were scant and structurally abnormal. The Golgi complex was rarely prominent; microbodies were common; and lysosomes were infrequent. Other organelles included glycogen particles, liquid droplets, long microtubules, and 50 A filaments. Filopodia were common as were rudimentary intercellular junctions. These

ells closely resemble those of secondary mesenchyme nd immature and neoplastic fibroblasts. It is conluded that fetal mesenchymal hamartoma is a secoناry mesenchymal tumor.

2794 FAMILIAL TRANSITIONAL CELL CARCINOMA OF THE BLADDER. (Eng.) McCullough, D. L. Univ. California Sch. Med., San Diego); Lamm, D. L.; cLaughlin, A. P., III; Gittes, R. F. *J. Urol.* 13(5):629-635; 1975.

family in which transitional cell carcinoma of the bladder was found in 6 of 34 members who lived beond age 30 is described; possible etiologic factors, ncluding heredity, carcinogen-exposure, immunologic ompetence, and tryptophan metabolism, are also evaluated. A genealogy involving 185 family members n six generations was created. Medical histories ere obtained and documented where possible, and evidence of exposure to carcinogens was recorded. Histological sections showing transitional cell tuors from five patients were examined. No evidence as found of common exposure to carcinogens; 2 of the 6 had no exposure to tobacco. Three cases occurred among brothers in the first generation; two of the second generation patients were sons of one of these brothers. A daughter of another brother as affected. Screening evaluations were performed on the immediate relatives of the second generation brother pair. In this group no additional tumors were found; urinary cytology and urinalysis were normal. Tryptophan metabolism was normal in all family members, including one of the patients who has had continued recurrences of transitional cell carcinoma. Histocompatibility antigen was compatible with the family relationships reported. Immunologic competence was normal in all unaffected family members, except a daughter of the patient with recurring carcinoma who showed impaired lymphocyte reactivity on repeated testing. Although several previous studies attempting to relate bladder cancer to heredity have failed to demonstrate any statistically significant correlation, the transmission of bladder carcinoma in this family is compatible with an autosomal dominate trait. Since the parent generation was unaffected, the authors suggest that either a mutation occurred in one of the parents or that one parent carried the mutation without expressing it. The mutation passed to approximately half of the offspring, with a high incidence of physical expression. The gene may not be entirely specific, as associated malignancies in patients and other carcinomas in unaffected relations occurred in those who might be expected to have inherited the genetic mutation.

2795 FURTHER OBSERVATIONS ON CARCINOMA *IN SITU* OF THE URINARY BLADDER: SILENT BUT EXTENSIVE INTRAPROSTATIC INVOLVEMENT. (Eng.) Seemayer, T. A. (3775 Univ. St., Montreal, Quebec, Canada); Knaack, J.; Thelmo, W. L.; Wang, N. S.; Ahmed, M. N. *Cancer* 36(2):514-520; 1975.

Prostatic tissues of seven patients with carcinoma *in situ* of the urinary bladder without clinical and/or histologic papillary tumors were examined. The tissue was serially sectioned and examined histologically. Of the seven patients, five had silent but extensive intraductal prostatic involvement. In three of these, the carcinoma *in situ* was associated with microinvasion. The mean age at the time of diagnosis was 68 yr. All had symptoms characteristic of carcinoma *in situ*, including hematuria, dysuria, and urgency. In three patients the prostatic involvement was diagnosed on transurethral resection. In two patients it was discovered only after radical cystectomy. The prostatic involvement was neither suspected clinically nor has it been previously emphasized. Although three patients were alive, apparently free of disease up to 15 mo postcystectomy, two had died, one of metastatic disease. The remaining patient was alive, but had clinical symptoms indicative of persistent disease. The importance of prostatic assessment in the evaluation of the patient with carcinoma in situ of the urinary bladder is emphasized.

2796 ULTRASTRUCTURE OF OVARIAN TERATOMAS IN LT MICE. (Eng.) Damjanov, I. (Dept. Pathology, UCONN Health Center, Farmington, Conn. 06032); Katic, V.; Stevens, L. C. *Z. Krebsforsch.* 83(4):261-267; 1975.

The ultrastructure of ovarian teratomas in LT mice was investigated with emphasis on tumor stem cells. These cells formed nests consisting of undifferentiated embryonic cells in the center with more differentiated cells toward the periphery. The stem cells contained intracisternal A-type viral particles. Ultrastructurally the stem cells of the ovarian teratomas did not differ from stem cells of testicular or embryo-derived teratomas. The cells were, however, distinct from the cleavage stage embryonic cells and/or the unfertilized ovum from which they arose. Both cytologically and developmentally, the stem cells corresponded to ectodermal embryonic cells from the egg-cylinder, the most advanced development stage of parthenotes previously observed in the ovary of LT mice. The finding of A-type particles in the stem cells indicated that they had passed the three to four cell embryo stage of development.

2797 OCCURRENCE OF OTHER ENDOCRINE TUMOURS IN PRIMARY HYPERPARATHYROIDISM. (Eng.) Taylor, S. (Royal Postgraduate Medical Sch. Hammersmith Hosp., London W12 OHS, England); Boey, J. H.; Cooke, T. J. C.; Gilbert, J. M.; Sweeney, E. C. *Lancet* 2(7939):781-784; 1975.

A series of 119 patients who underwent parathyroidectomy between 1955 and 1975 were followed up in order to determine the occurrence of multiple endocrine adenomatosis (MEA). The patients were deemed to show evidence of an associated endocrinopathy on the basis of the following criteria: clinically overt disease (e.g., acromegaly), radiological enlargement of the pituitary, biochemical findings of raised plasma-hormone concentration, and postmortem discovery of hyperplasia or adenoma of an endocrine gland. Twenty-one patients (17.5%) were

found to have evidence of associated endocrine disease and were deemed to have MEA. The clinical pattern of hypercalcemia in no way distinguished these patients from other hyperparathyroid patients. MEA was most commonly found in patients with several diseased parathyroid glands. The results suggest that MEA is more common in hyperparathyroid patients than earlier reports have indicated.

2798 PITUITARY TUMOR WITH PRIMARY HYPOTHYROIDISM; POSSIBLE ETIOLOGIC RELATIONSHIP. (Eng.) Balsam, A. (Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, N.Y. 10467); Oppenheimer*, J. H. *N.Y. State J. Med.* 75(10):1737-1741; 1975.

The case of a 59-yr-old woman with a pituitary tumor, chiasmatic compression, and presumed secondary hypothyroidism was reevaluated. Lack of augmentation of the 24-hr radioiodine uptake following the administration of exogenous thyroid stimulating hormone (TSH) had previously been attributed to thyroidal atrophy due to prolonged absence of thyrotrophic stimulation. However, the new finding of elevated plasma levels of endogenous TSH (25 μU/ml) which were suppressed by thyroid hormone replacement 25 gr./day, established the diagnosis of primary hypothyroidism. These findings prompted a review of sella x-ray films of 40 cases of primary hypothyroidism; four patients had enlargement of the sella turcica. The development of reactive pituitary enlargement in primary hypothyroidism may be more frequent than was previously suspected.

2799 SMALL CELL MALIGNANT TUMORS OF THE THYROID: A LIGHT AND ELECTRON MICROSCOPIC STUDY. (Eng.) Cameron, R. G. (Pathological Inst., 3775 University St., Montreal, Province of Quebec, Canada); Seemayer*, T. A.; Wang, N.-S.; Ahmed, M. N.; Tabah, E. J. *Hum. Pathol.* 6(6):731-740; 1975.

Observations obtained with the light and electron microscopes on three small cell malignant tumors involving the thyroid gland are presented. The case reports of the patients; an 86-yr-old woman, a 61-yr-old man, and a 57-yr-old woman; are also presented. In each tumor numerous similarities were present on light microscopic analysis rendering interpretation difficult. In the 86-yr-old woman the small cells were identified by electron microscopy as moderately well differentiated lymphocytes. This tumor occurred as a locally invasive thyroid tumor, subsequently involving distant sites, including the liver, spleen, lymph nodes, and soft tissue. The tumor repeatedly regressed following radiotherapy. The patient eventually died with disseminated lymphocytic lymphoma. In the man, the thyroid tumor also locally invasive was composed principally of neoplastic epithelial cells, which were identified with the electron microscope. This patient responded poorly to radiation and died within a year after diagnosis. The third patient presented with an enlarging thyroid mass, which ultrastructurally was found to be composed principally of well differentiated lymphocytes. Subsequent clinical evaluation established a diagnosis of chronic lymphocytic leukemia. Small cell malignant tumors of the thyroid represent a difficult diagnostic problem for surgical pathologists. Ultrastructural study is a useful adjunct in the differentiation of these tumors.

2800 VITILIGO AND MALIGNANT MELANOMA. (Eng.) Fodor, J. (Natl. Cancer Inst., Budapest, Hungary); Bodrogi, I. *Neoplasma* 22(4): 445-448; 1975.

In 4 of 6 cases of vitiligo and malignant melanoma, the latter was detected a few years after onset of vitiligo (ages 44-73 yr). The authors conclude that old-age vitiligo may be a skin marker of malignant neoplasm.

2801 MULTIFOCAL SCLEROSING OSTEOID OSTEOMA (ONE CASE). (Rus.) Selivanov, V. P. (Novokuznetsk Municipal Clinical Hosp. No. 1, U.S.S.R.); Fetinin, V. A. *Vopr. Onkol.* 21(9):94-95; 1975.

2802 METASTASES TO THE BONES OF THE HAND. (Eng.) Kumar, P. P. (Howard Univ. Coll. Medicine, Washington, D.C.). *J. Natl. Med. Assoc.* 67(4):275-276; 1975.

2803 BONE LESIONS OF MALIGNANT LYMPHOMA. (Jpn.) Watanabe, T. (Dept. of Radiology, Shinshu Univ., Asahi 3-1-1, Matsumoto, Japan). *Nippon Acta Radiol.* 35(3):111-118; 1975.

2804 RHABDOMYOSARCOMA OF THE BRAIN: CASE REPORT. (Eng.) Matsukado, Y. (Kumamoto Univ. Medical Sch., Kumamoto, Japan 860); Yokota, A.; Marubayashi, T. *J. Neurosurg.* 43(2):215-221; 1975.

2805 MEDULLOBLASTOMA IN TWO BROTHERS. (Eng.) Yamashita, J. (Kyoto Univ. Medical Sch., Sakyoku, Kyoto, Japan 606); Handa, H.; Toyama, M. *Surg. Neurol.* 4(2):225-227; 1975.

2806 "MALIGNANT LYMPHOMA" OF THE BRAIN FOLLOWING RENAL TRANSPLANTATION. (Eng.) Kersting, G. (Institut fur Neuropathologie d. Univ., Annaberger Weg, 5800 Bonn-Venusberg, West Germany); Neumann*, J. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:131-133; 1975.

2807 CYTOMEGALOVIRUS AND LYMPHOMA IN A PEDIATRIC TRANSPLANT RECIPIENT [letter to editor]. (Eng.) Matas, A. J. (Mayo Memorial Bldg., Univ. Minnesota, Minneapolis, Minn. 55455); Simmons, R. L.; Kersey, J. H.; Kjellstrand, C. M.; Najarian, J. S. *J. Pediatr.* 87(3):494-495; 1975.

2808 PRIMARY LYMPHOMAS OF THE CENTRAL NERVOUS

SYSTEM; *IN VITRO* CULTURE OBSERVATIONS. (Eng.) Gazso, L. (Inst. Neurosurgery, Amerikai ut 57, H-1145 Budapest, Hungary); Slowik, F. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:103-106; 1975.

2809 A COMPARISON OF THE FINE STRUCTURE OF MALIGNANT LYMPHOMA AND OTHER NEOPLASMS IN THE BRAIN. (Eng.) Hirano, A. (Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, N.Y. 10467). *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:141-145; 1975.

2810 PRIMARY AND BORDERLINE BRAIN LYMPHOSARCOMA: A NEUROPATHOLOGICAL REVIEW OF NINE CASES. (Eng.) Foncin, J.-F. (Laboratoire de Physiologie, Hopital de la Salpetriere, Paris 13 E, 47, Blvd. de l'Hopital, France); Faucher, J.-N. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:107-113; 1975.

2811 ANALYSIS OF CEREBROSPINAL FLUID CELLS FROM AN AMERICAN CHILD WITH BURKITT'S LYMPHOMA. (Eng.) Fuchs, H. B. (Cardinal Glennon Mem. Hosp. Child., St. Louis, Mo.); Rosan, R. C. *Am. J. Clin. Pathol.* 64(2):238-240; 1975.

2812 NEOPLASTIC INVOLVEMENT OF THE CNS IN GENERALIZED LYMPHOMAS. (Eng.) Janisch, W. (Pathologisches Institut der Martin-Luther-Universitat Halle-Wittenberg, DDR 402 Halle/S., Leninallee 14, East Germany); Gerlach, H.; Remus, I. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:81-84; 1975.

2813 LIGHT-AND ELECTRON MICROSCOPIC STUDIES IN HEMOBLASTOSIS WITH CNS-DISORDER. (Eng.) Mobius, W. (Med. Universitatsklinik Freiburg, Hugstetter Strasse 55, D-7800 Freiburg, West Germany); Stang-Voss, C.; Hennekeuser, H. H. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:193-198; 1975.

2814 HUMAN AND EXPERIMENTAL RETICULUM CELL SARCOMA (MICROGLIOMA) OF THE NERVOUS SYSTEM. (Eng.) Cravioto, H. (N.Y.U. Medical Center, 550 First Ave., New York, N.Y. 10016). *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:135-140; 1975.

2815 PATHOLOGY OF PRIMARY RETICULUM CELL SARCOMA OF THE HUMAN CENTRAL NERVOUS SYSTEM. (Eng.) Reznik, M. (Institut de Pathologie, Universite de Liege, Rue des Bonnes Villes, I, 4000 Liege, Belgium). *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:91-94; 1975.

2816 CLINICAL AND PATHOLOGICAL STUDIES IN A CASE OF RETICULUM CELL SARCOMA. (Eng.) Inose, T. (Yokohama City Univ. Sch. Medicine, Urafune-cho, Minami-ku, Yokohama, Japan); Kinoshita, J. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:209-212; 1975.

2817 MICROGLIOMA AND/OR RETICULOSARCOMA OF THE NERVOUS SYSTEM. (Eng.) Polak, M. (Registro Latino Americano de tumores del Systema Nervioso, Terrada 1164 Buenos Aires, Argentina). *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:115-118; 1975.

2818 THE CLASSIFICATION OF MICROGLIOMATOSIS WITH PARTICULAR REFERENCE TO DIFFUSE MICROGLIOMATOSIS. (Eng.) Adams, J. H. (Inst. Neurological Sciences, Southern General Hosp., Glasgow G 51 4 TF, Scotland). *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:119-123; 1975.

2819 PRIMARY CEREBRAL RETICULOSIS AND PLASMA CELL DIFFERENTIATION. (Eng.) Vuia, O. (Inst. Neuropathology, Justus Liebig Univ., Arndtstrasse 16, D-63 Giessen, West Germany). *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:161-166; 1975.

2820 PATTERNS OF PROLIFERATION IN CEREBRAL LYMPHORETICULAR TUMOURS. (Eng.) Barnard, R. O. (Maida Vale Hosp., London, W. 9 ITL, England); Scott, T. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:125-130; 1975.

2821 DIFFUSE RETICULOSIS WITH LEUKOMALACIA. (Eng.) Liss, L. (Neuropathology Div., Upham Hall, Ohio State Univ., Columbus, Ohio 43210); Gogate, S. A. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:257-260; 1975.

2822 PRIMARY INTRACRANIAL OLFACTORY ESTHESIONEUROEPITHELIOMA. (Jpn.) Kinoshita, K. (Kumamoto Univ. Medical Sch., Kumamoto, Japan); Marubayashi, T.; Tokuda, H.; Matsukado, Y. *No To Shinkei* 27(1):39-47; 1975.

2823 BREAST CANCER. (Ita.) Bianucci, P. (Ente Ospedaliero San Paolo Di Savona, Piazza Liguria, 3/3 17012 Albissola Mare, Savona, Italy). *Cancro* 27(6):345-351; 1974.

2824 A SARCOMATOUS METASTASIS OF A CARCINOMA OF THE BREAST. (Ger.) Korb, G. (Stadtisches Krankenhaus, Pathologisches Institut, D-8480 Weiden i.d. Oberpfalz, Bismarckstrasse 30, West Germany); Weiss, R. *Z. Krebsforsch.* 83(3):251-253; 1975.

2825 ELECTRONMICROSCOPIC STUDIES ON SOLID MAMMARY CARCINOMAS IN BITCHES. (Ger.) von Bomhard, D. (Institut fur Allgemeine Pathologie und Pathologische Anatomie der Tierarztlichen Fakultat der Universitat, D-8000 Munchen 22, Veterinarstrasse 13, West Germany); Raddatz, R. Raddatz, R. *Z. Krebsforsch.* 83(2):129-143; 1975.

2826 A CASE OF 'CROHN'S CARCINOMA'. (Eng.) Fleming, K. A. (Univ. Dep. Pathol., Glas-

gow R. Infirm., Scotland); Pollock, A. C. *Gut* 16 (7):533-537; 1975.

2827 CARCINOMA COMPLICATING CROHN'S DISEASE: REPORT OF SEVEN CASES AND REVIEW OF THE LITERATURE. (Eng.) Lightdale, C. J. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, N.Y. 10021); Sternberg, S. S.; Posner, G.; Sherlock, P. *Am. J. Med.* 59(2):262-268; 1975.

2828 POLYPOSIS OF THE LARGE BOWEL AND CANCER: LONGITUDINAL STUDIES [abstract]. (Eng.) Burbige, E. J. (Dept. of Med., The Johns Hopkins Univ., Baltimore, Md.); Cohen, S. B.; Krush, A. J.; Levin, L. S.; Wennstrom, J.; Murphy, E.; Milligan, F. D. *Gastroenterology* 68(4/Part 2):869; 1975.

2829 ADENOCARCINOMA OF THE JEJUNUM ASSOCIATED WITH NONTROPICAL SPRUE. (Eng.) Petreshock, E. P. (Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y. 11040); Pessah, M.; Menachemi, E. *Am. J. Dig. Dis.* 20(8):796-802; 1975.

2830 CANCER OF THE GASTRIC STUMP FOLLOWING OPERATIONS FOR BENIGN GASTRIC CANCER OR DUODENAL ULCERS. (Eng.) Gazzola, L. M. (30 rue Jean Violette, 1205 Geneva, Switzerland); Saegesser, F. *J. Surg. Oncol.* 7(4):293-298; 1975.

2831 EXTRAMAMMARY PAGET'S DISEASE AND ANAPLASTIC BASALOID SMALL-CELL CARCINOMA OF THE ANUS: REPORT OF A CASE. (Eng.) Jackson, B. R. (St. Vincent's Hosp., Los Angeles, Calif.). *Dis. Colon Rectum* 18(4):339-345; 1975.

2832 DOUBLE AND MULTIPLE CARCINOMAS OF THE COLON [abstract]. (Dut.) Heystraten, F. M. J. (Nijmegen, Netherlands); Schillings, P. H. M.; Rosenbusch, G. *Ned. Tijdschr. Geneeskd.* 119(37):1440-1441; 1975.

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2875 NATURAL HISTORY OF FAMILIAL MEDULLARY CARCINOMA OF THE THYROID GLAND (MCT)-PHEOCHROMOCYTOMA SYNDROME AND THE IDENTIFICATION OF PRENEOPLASTIC STAGES BY SCREENING TESTS [abstract]. (Eng.) Gagel, R. F. (Tufts N. Engl. Med. Cent., Boston, Mass.); Melvin, K. E. W.; Tashjian, A., Jr.; Feldman, Z.; Wolfe, H.; DeLellis, R.; Cervi-Skinner, S.; Riechlin, S. *Clin. Res.* 23(3): 437A; 1975.

2876 THE PLACE OF SURGERY IN NODULAR THYROID DISEASE. (Eng.) Dent, D. M. (Dep. Surg., Univ. Cape Town, South Africa); Miller, A.; Louw, J. H. *S. Afr. Med. J.* 49(10):354-357; 1975.

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2878 ASSOCIATED CONGENITAL MALFORMATIONS IN RETINOBLASTOMA. (Eng.) Bonaïti-Pellié, C. (Clinique de Génétique Médicale, Unité de Recherches de Génétique Médicale I.N.S.E.R.M., Hopital des Enfants-Malades, Paris, France); Briard-Guillemot, M. L.; Feingold, J.; Frézal, J. *Clin. Genet.* 7(1):37-39; 1975.

2879 MIXED LYMPHOCYTE CULTURE DETERMINANTS AND C2 DEFICIENCY: LD-7a ASSOCIATED WITH C2 DEFICIENCY IN FOUR FAMILIES. (Eng.) Fu, S. M. (Rockefeller Univ., New York, N.Y. 10021); Stern, R., Kunkel, H. G.; Dupont, B.; Hansen, J. A.; Day, N. K.; Good, R. A.; Jersild, C.; Fotino, M. *J. Exp. Med.* 142(2):495-506; 1975.

See also:

* (Rev): 2405, 2410, 2411, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446
* (Chem): 2454, 2461, 2490, 2523, 2548
* (Phys): 2562, 2564, 2565, 2571
* (Viral): 2636
* (Immun): 2712, 2717, 2737, 2741
* (Epid): 2880, 2892, 2894, 2901

2880 FAMILIAL LEUKAEMIA: A STUDY OF 909 FAMILIES. *(Eng.)* Gunz, F. W. (Sydney Hosp., Sydney, N.S.W. 2000, Australia); Gunz, J. P.; Veale, A. M. O.; Chapman, C. J.; Houston, I. B. *Scand. J. Haematol.* 15(2):117-131; 1975.

A family survey was conducted among 909 patients with leukemia of all types, with the purpose of establishing the incidence of further cases of leukemia among relatives. Among 41,807 relatives 8,349 were deceased, and the cause of death was objectively confirmed in 5,011. Seventy-two patients had one or more relatives with leukemia. First degree relatives with leukemia were much more frequent in families of patients with chronic lymphocytic leukemia than in those of patients with chronic granulocytic leukemia. The incidence of leukemia among first degree relatives was established to be 2.8-3.0 times, among more distant relatives about 2.3 times, and overall about 2.5 times that expected. This excess is of the order of that observed in relatives of patients with solid tumors. Genetic factors may have accounted for much of the excess incidence in chronic lymphocytic and acute leukemia, but there was little evidence for a genetic background in chronic granulocytic leukemia. With the possible exception of one family with multiple cases, a simple Mendelian mechanism did not appear to be involved in the leukemia families investigated. It appears more likely that a polygenic mechanism led to a heightened susceptibility to the disease in these families.

2881 CANCER BY COUNTY: NEW RESOURCE FOR ETIOLOGIC CLUES. (Eng.) Hoover, R. (Epidemiology Branch, Natl. Cancer Inst., Bethesda, Md. 20014); Mason, T. J.; McKay, F. W.; Fraumeni, J. F., Jr. *Science* 189(4207):1005-1007; 1975.

To provide leads to the causes of cancers, cancer-mortality rates were collected for the 3056 counties of the contiguous U. S. The age-standardized mortality rates for 35 cancer sites were calculated from the age-, race-, and sex-specific rates for 1950-1969. The distribution of bladder cancer in white men so obtained is clustered in areas with heavy industry; this pattern was not duplicated in females. To characterize the possible hazards, 64 areas were selected in which: bladder-cancer mortality for men was significantly higher than the national rate, the male-to-female ratio of bladder cancer mortality was higher than the national ratio, and the lung-cancer rate among men did not differ significantly from the national rate. These criteria selected areas where bladder cancer is more likely to be related to industrial exposure than to cigarette smoking. The patterns obtained indicate that automobile and nonelectrical-machinery manufacturing are correlated with high incidences of bladder cancer. The known association with chemical industry was confirmed. Mapping of stomach-cancer mortality rates showed high rates in major cities and areas characterized by low socioeconomic class, but also in rural counties with notable populations of Russian, Austrian, Scandinavian, and German descent.

2882 EPIDEMIOLOGICAL STUDIES OF α-FETOPROTEIN AND HEPATITIS B ANTIGEN IN TOMIE TOWN, NAGASAKI, JAPAN. *(Eng.)* Koji, T. (Nagasaki Univ. Sch. Medicine, Nagasaki, Japan); Munehisa, T.; Yamaguchi, K.; Kusumoto, Y.; Nakamura, S. *Ann. N.Y. Acad. Sci.* 259:239-247; 1975.

Annual mass physical examinations were conducted on 1,582 individuals (613 male, 969 female, 30-84 yr old) in Tomie Town, Japan in order to screen for liver diseases and for the presence of α-fetoprotein, hepatitis B antigen and hepatitis B antibody. The clinical protocol involved a medical history, a physical examination and five laboratory tests: SGOT, glutamic pyruvic transaminase, thymol turbidity, zinc sulfate turbidity, and alkaline phosphatase. Further examinations were performed on individuals in whom hepatomegaly was detected or who showed abnormal clinical findings. Among 668 adult subjects (246 male, 422 female), the hepatitis B antigen and antibody levels were measured by immune adherence hemagglutination and passive hemagglutination. Serum α-fetoprotein levels were estimated by hemagglutination. There were 484 cases (30.6%) of hepatomegaly and 208 (13.1%) cases of abnormal liver function. The number of individuals who had both conditions was 101 (6.4%). Among the 81 subjects who underwent liver biopsy, seven cases of liver cirrhosis and one hepatoma were observed. Ten cases of chronic hepatitis and 40 cases of nonspecific liver fibrosis were also seen. The incidence of positive hepatitis B antigen and hepatitis B antibody serum levels were 5.7% and 25.4%, respectively (the highest rates in Japan). Of five cases of liver cirrhosis or hepatoma, four were positive for hepatitis B antigen. Two of 668 subjects were positive for α-fetoprotein, showing radioimmunoassay serum concentrations of 130 and 260 ng/ml, respectively. The first subject had clinically diagnosed liver cirrhosis with hepatoma but soon died; the second is a case with previously unsuspected hepatoma who survived surgery, and for whom a brief case report is presented. In both hepatoma cases the serum was positive for hepatitis B antigen. These findings suggest, but do not prove, a possible role for hepatitis B antigen as one of the etiological factors in liver disease. The fact that one clinically latent hepatoma patient was detected by the α-fetoprotein assay and underwent a successful operation verifies the validity of the α-fetoprotein assay for the early diagnosis of hepatoma.

2883 MALIGNANT TUMORS IN AMERICAN BLACK AND NIGERIAN CHILDREN: A COMPARATIVE STUDY. *(Eng.)* Olisa, E. G. (Dept. Pathology, Howard Univ., Washington, D.C. 20001); Chandra, R.; Jackson, M. A.; Kennedy, J.; Williams, A. O. *J. Natl. Cancer Inst.* 55(2):281-284; 1975.

Results of a study on the relative frequencies of tumors in 162 American black and 1,325 Nigerian children were compared with data from the Childhood Cancer Registries in Manchester, United Kingdom (994 children), and Kampala, Uganda (776). The American black child living in Washington, D.C. and the Caucasian child living in Manchester had simi-

lar high frequencies for leukemia (27.8% and 29.5%, respectively) and glioma (11.2% and 17.0%, respectively), whereas the incidence of lymphoma (9.8% and 8.7%, respectively) and retinoblastoma (4.9% and 3.1%, respectively) was low. African children living in Nigeria or Uganda had the opposite frequency patterns. These were, for Uganda and Nigeria respectively, 7.1% and 4.5% leukemia; 49.2% and 59.0% lymphoma; 1.3% and 2.2% gliomas; and 7.4% and 7.4% retinoblastoma. These differences in frequencies of tumors between two ethnologically related population groups (American black and Nigerian) suggest the influence of environmental factors in the etiology of these tumors, even though exposure to environmental carcinogens was short. The rarity of Ewing's sarcoma and testicular tumors in American black (0.6% and 0%, respectively) and Nigerian children also suggest a genetic influence.

2884 MALIGNANT MELANOMA IN THE IGBOS OF NIGERIA. (Eng.) Onuigbo, W. I. B. (General Hosp., Enugu, Nigeria). *Br. J. Plast. Surg.* 28(2):114-117; 1975.

Of 21 cases of malignant melanoma occurring in the Igbos of Nigeria 17 were on the foot; 11 of these were on the sole. This result supports the conclusion that Negroes tend to have the disease in the non-pigmented parts. Wearing shoes might decrease the incidence of melanoma of the sole in undeveloped countries.

2885 PREVALENCE OF CARCINOMA OF THE PENIS WITH SPECIAL REFERENCE TO INDIA. (Eng.) Reddy, C. R. R. M. (D-8 Doctor's Colony, Visakhapatnam 530002, India); Raghavaiah, N. V.; Mouli, K. C. *Int. Surg.* 60(9):474-476; 1975.

The frequency of carcinoma of the penis throughout the world is tabulated and compared with similar data from 32 hospitals in India. There is a wide variation in the frequency of penile carcinoma in India, the disease ranking first among male cancers in some areas and tenth or lower in other areas. In Visakhapatnam, penile carcinoma accounted for 12.5% of male cancers and 5.5% of all cancers. The highest incidence was in Kurnool, where carcinoma of the penis accounted for 13.8% of male cancers and 6.9% of all cancers. Hindus, who do not usually practice circumcision, predominate in India; however, in some regions with many Muslims (as in Kurnool) the frequency of penile carcinoma is high. In other Muslim areas, such as Hyderabad, the incidence is low. Other etiologic factors such as poor sexual hygiene may account for this variability in frequency. There was no relationship between the frequency of cervical and penile carcinomas.

2886 PROSTATIC MALIGNANCY IN INDIA. (Eng.) Raghavaiah, N. V. (New Padma Buildings, Maharanipet, Visakhapatnam 530002 Andhra Pradesh, India); Singh, S. M. *Int. Surg.* 60(9):482-485; 1975.

Clinicopathologic data are presented for 120 cases of carcinoma of the prostate diagnosed and treated at a New Delhi hospital between January 1, 1965 and June 30, 1972. The cases comprised 0.14% of all hospital admissions, 1.8% of all urological patients, and 22.5% of patients admitted with prostatic disease. The highest incidence of prostatic carcinoma was in patients aged 61-70 yr. The most common presenting symptom was prostatism followed by anemia. Hematuria was less frequent than in benign prostatic hypertrophy. In 80% of the cases, the prostate was hard and nodular and typical of malignancy; rectal palpation was the only investigation used to screen the majority of carcinoma cases. Histologically, 75% of the carcinoma were adenocarcinoma, 15.3% were anaplastic, and 0.7% were squamous cell carcinomas. Almost all the patients presented at a very late stage in the disease; hence, radical surgery was not feasible. Palliative treatment consisted of diethylstilbestrol therapy, bilateral orchidectomy, or estrogen administration (1-15 mg/day in divided doses). Results of treatment could not be assessed because 70-80% of the patients were not followed.

2887 EPIDEMIOLOGIC ASSOCIATION BETWEEN GONORRHEA AND PROSTATIC CARCINOMA. *(Eng.)* Heshmat, M. Y. (520 "W" St., N.W., Washington, D.C.); Kovi, J.; Herson, J.; Jones, G. W.; Jackson, M. A. *Urology* 6(4):457-460; 1975.

The relationship between gonorrheal infection and later development of prostatic carcinoma was assessed. Two methods included: (a) an associative study of the correlation between gonorrhea incidence and prostatic cancer mortality rates in Denmark, and (b) a retrospective epidemiologic study of patients with prostatic cancer and matching controls. Figures for the incidence of gonorrhea (1891-1940) and for mortality from prostatic cancer (1941-1970) were obtained for Denmark. Curves for gonorrhea incidence rates per 100,000 men and for death rates from prostatic cancer per 100,000 men were subjected to a time series analysis using a computer program. All patients with prostatic cancer diagnosed since 1973 in five hospitals in Washington, D.C. will be interviewed for a past history of gonorrhea. The curves for death rates from prostatic cancer and gonorrhea incidence rates in Denmark, over a span of 30 yr, matched well with a lag period of 45 yr. The retrospective study of 75 cancer patients and 75 age-matched controls demonstrated a statistically significant ($P < 0.05$) association between gonorrheal infection and subsequent development of prostatic cancer. The findings could be explained by two hypotheses: the viral-venereal theory, and the chronic prostatitis theory. A recent increase in the incidence of prostatic cancer in the U.S. could be the beginning of an epidemic.

2888 SOME MARITAL-SEXUAL CONCOMITANTS OF CARCINOMA OF THE CERVIX. (Eng.) Vincent, C. E. (Boeman Gray Sch. Med., Winston-Salem, N.C.); Vincent, B.; Greiss, F. C.; Linton, E. B. *South. Med. J.* 68(5):552-558; 1975.

Fifty patients were given four interviews concerning

their thoughts, feelings, and behavior, before, during, and after treatment of cervical cancer. They were poor white women, married at least once, from rural areas. Seventy-two percent of the women had not completed high school. They were equally treatable by surgery or radiotherapy. The patient's degree of enjoyment of coitus before diagnosis appeared to influence how early she reported symptoms such as postcoital or intermenstrual spotting. Those who indicated they did not enjoy coitus reported spotting sooner. The lower the woman's education and the greater her enjoyment of sex, the longer was her delay in reporting symptoms. Patients expressed a need for sex information to be given by the physician to husbands and wives together. Most women were eager to present themselves to their physicians with an image of self-control. For brief periods, however, they responded to support and comfort from a female relative, friend or interviewer. They expressed fears related to waiting for the diagnosis and treatment, which persisted throughout treatment. Up to a year after treatment, the question of whether or not she is cured causes further anxieties in the patient.

2889 BRONCHIAL CANCER -- A CLINICAL AND PATHOLOGICAL STUDY. II. FREQUENCY ACCORDING TO AGE AND SEX DURING A 12-YEAR PERIOD. (Eng.) Berge, T. (Dept. Pathology, Karusjukhuset, 541 01 Skovde, Sweden); Toremalm, N. G. *Scand. J. Respir. Dis.* 56(2):120-126; 1975.

A necropsy series of bronchial cancer combined with a retrospective clinical study comprising 747 cases of bronchial cancer from a defined population is described. The increase in the frequency of bronchial cancer during three successive 3-yr periods is 45, 86 and 146%, respectively, if the 1958-1960 frequency is set to 100%. The relative increase was exactly the same in both sexes and for tumors of two main histologic groups. This may be explained by the assumption that the female population today has smoked cigarettes for a sufficiently long period to stimulate the development of bronchial cancer. It appears that frequency-figures are too low in earlier series and may be too high (because of clinical overdiagnosis) in more recent series.

2890 RECENT DATA ON THE EPIDEMIOLOGY OF MALIGNANT MELANOMA. (Eng.) Elwood, J. M. (Dept. of Epidemiology and Community Medicine, Univ. of Ottawa, Ottawa, Ontario, Canada); Lee, J. A. H. *Semin. Oncol.* 2(2):149-154; 1975.

Recent data on the epidemiology of malignant melanoma are reported. Mortality rates rose approximately 3-9%/yr over the last 30 yr. In some countries (e.g., Canada), the rate of increase was greater than that for any other tumor except lung cancer in males. The rise in incidence and mortality was greater in young people than those over 65 yr; thus, people born in more recent years have higher incidence and mortality rates from melanoma at all ages than those born earlier. The increase in incidence and mortality rates was greater for certain body sites, indicating that the site of melanoma distribution has changed. According to a Connecticut tumor registry (1935-1972), there was a small increase in the incidence of tumors of the head and neck, a striking increase in tumors of the lower limbs of females, the trunk in men, and the upper limbs in both sexes. The site-sex differences gave some clues to possible etiology; it appeared that the change was greatest in those sites where exposure to the sun was increased as a result of changes in clothing and recreational habits after World War II. This was demonstrated by a study in Queensland, Australia (1963-1967), where the incidences of melanoma by body site showed that areas with significant excesses of melanomas were usually exposed areas (face, leg, neck, and back in men). The frequency of melanocytes varied with the region and the thickness of the skin. These data suggest a dose-response relation between UV radiation, exposure, and the development of melanoma; environmental changes that produce even small increases in UV radiation should be viewed with concern. The relation of skin cancer mortality rates to latitude within North America is also described. Melanoma mortality and latitude exhibited a linear relation over the 48 states and ten Canadian provinces; mortality decreased (22 deaths per million to seven deaths per million) as the degree of north latitude increased (25-55°). The death rates were greater for males than for females, suggesting the action of a hormonal or other biochemical factors.

2891 BURKITT'S LYMPHOMA. (Eng.) Vianna, N. J. (Cancer Control Bureau, New York State Dept. Health, Albany, N.Y.). In: *Lymphoreticular Malignancies: Epidemiologic and Related Aspects.* Baltimore, University Park Press, 1975, pp. 49-59.

Various etiologic and epidemiologic features of Burkitt's lymphoma are presented. Contrasting incidence patterns were studied in relation to the histologic similarity of Burkitt's tumor in endemic and nonendemic areas. In tropical Africa, it is the most frequently encountered childhood malignancy; it is endemic in Uganda and New Guinea. In Canada, Great Britain, the U.S., and Brazil, it occurs only sporadically. Burkitt's lymphoma demonstrates a climatic dependence. In Africa, it occurs with greatest frequency in regions with a mean temperature of 60 F during the coldest month. Burkitt's lymphoma occurs around lakes, but not in regions with an altitude over 5000 ft. Evidence of time-space clustering has been variable; it was demonstrated in the West Nile district and Bwamba, but not in the North Mara district in Tanzania. Additional evidence is presented for an epidemic drift of this disorder, suggesting that some environmental agent had moved through the community. Studies in several countries have indicated that the prevalence of Epstein-Barr virus (EBV) antibody varies according to the level of socio-economic development, and that EBV is not solely responsible for Burkitt's lymphoma. One study in Uganda suggests a close association between the incidence of Burkitt's lymphoma and malaria; in areas where malaria control has been instituted, Burkitt's lymphoma rates have decreased. The re-

lation between Burkitt's lymphoma and acute lymphatic leukemia is also discussed. One hypothesis suggests that they are alternative forms of one another. This theory is based on a study which indicated that lymphoblastic leukemia is the major childhood lymphoproliferative malignancy in the northern hemisphere; in much of Africa and New Guinea, however, Burkitt's lymphoma predominates. Other studies suggest that while a deficiency in child lymphatic leukemia in certain African countries does exist, it is not inversely related to the incidence of Burkitt's lymphoma. These contrasting findings demonstrate the need for additional studies to elucidate the true nature of Burkitt's lymphoma.

2892 PROPORTIONAL MORTALITY AMONG ALCOHOLICS. *(Eng.)* Monson, R. R. (Harvard Sch. Public Health, 677 Huntington Ave., Boston, Mass. 02115); Lyon, J. L. *Cancer* 36(3):1077-1079; 1975.

To test the hypothesis that there is a positive association between chronic alcoholism and carcinoma of the pancreas, the mortality experience of 1,382 chronic alcoholics (1,139 men and 243 women) was studied. Analysis was limited to a comparison of observed and expected proportional mortality of different causes of death in the 894 Caucasians who were known to have died. For carcinoma of the pancreas, three deaths were observed and 5.2 were expected. The observed/expected ratios for other causes of death, including other sites of cancer, were in accordance with prior studies, and there does not appear to be an association between alcohol consumption and cancer of the pancreas.

2893 ORAL CANCER AND PRECANCEROUS LESIONS IN 57,518 INDUSTRIAL WORKERS OF GUJARAT, INDIA. *(Eng.)* Smith, L. W. (Government Dental Coll. and Hosp., Ahmedabad-380 016 India); Bhargava, K.; Mani, N. J.; Malaowalla, A. M.; Silverman, S., Jr. *Indian J. Cancer* 12(2):118-123; 1975.

The objectives and results of a study of oral cancer and precancerous lesions in a selected population of 57,518 cohorts are reported. The objectives were (a) to determine the prevalence of oral and oropharyngeal cancer and precancerous lesions, and (b) to describe the relationship of oral and oropharyngeal cancer and lesions. All subjects were 35 yr of age or older. An examination of lips, oral cavity, oral pharynx and lymph node palpability was made. A chart was kept for data on specific lesions, and a biopsy was performed when possible. Men made up 95% of the population ranging in age from 35-83 yr. As literacy increased there was a corresponding decrease in the prevalence of leukoplakia, nicotine, stomatitis, and leukoedema. Most participants were Hindus (86%). No association was made between the use of chillies in food preparation and oral lesions. Ninety-three percent of the cohorts cleaned their teeth once a day and used a twig chewed in the form of a brush known as a "Datan". Twenty-nine cases of cancer were diagnosed along with 69 cases of epithelial dysplasia. Of the total study population, 28.3% had lesions. Of the lesions observed, 52.5% were nicotine stomatitis, and 32.1% were leukoplakia. The rate of oral cancer was 50.4 per 100,000. The high rate of oral cancer and precancerous lesions appears due to smoking and chewing habits of the study population. A close relationship existed between nicotine stomatitis and smoking; leukoedema also appeared to be related to a lesser extent.

2894 ADENOCARCINOMA OF THE NOSE AND PARANASAL SINUSES IN WOODWORKERS IN THE STATE OF VICTORIA, AUSTRALIA. *(Eng.)* Ironside, P. (Cancer Inst., 481 Little Lonsdale St., Melbourne 3000, Australia); Matthews, J. *Cancer* 36(3):1115-1121; 1975.

In view of findings in other countries, an investigation was carried out in Australia to determine whether or not adenocarcinoma of the nose and sinuses is associated with occupational exposure to wood dust. The case index of the Cancer Institute of Victoria contained 19 cases of adenocarcinoma of the nose and paranasal sinuses. Eighteen cases occurred in men and one occurred in a woman. Routine questioning of these patients revealed an occupation involving woodworking in seven cases, whereas among 80 cases of other malignant tumors of the nose and sinuses there were only four who had been woodworkers. Among the patients with adenocarcinoma of the nose and sinuses, there was a significantly higher proportion of woodworkers than in the general population. No tumors of specific salivary type were associated with exposure to wood dust. The findings are consistent with European reports associating nasal adenocarcinoma with wood dust, but whereas the workers at risk in Europe are mainly in the furniture industry, some of the workers affected in Victoria have been sawmillers or carpenters.

2895 THE OCCUPATION OF FISHING AS A RISK FACTOR IN CANCER OF THE LIP. (Eng.) Spitzer, W. O. (Faculty Medicine, Memorial Univ. Newfoundland, St. John's, Newfoundland); Hill, G. B.; Chambers, L. W.; Helliwell, B. E.; Murphy, H. B. *N. Engl. J. Med.* 293(9):419-424; 1975.

A project that included a case-control study and a cohort analysis was undertaken in Newfoundland to study the role of commercial fishing and related factors in the development of lip cancer. The cases were 366 patients with the diagnosis of squamous cell carcinoma of the lip and three control groups: (a) 132 patients with squamous cell carcinoma of the oral cavity, (b) 81 patients with squamous cell carcinoma of the skin of the head and neck, and (c) 210 randomly selected men, matched for age and geographic location. Household survey data were linked with cancer-registry and census data. In comparison with other men, fishermen had a probability of development of lip cancer that was 1.5 times higher (by the case-control method, $P < 0.05$) or 4.4 times higher (by cohort analysis, $P < 0.001$). Despite the effect of pipe smoking, "outdoorness" and age on the development of lip cancer in general, the occupation of fishing was an additional, independent contribution to the risk. Unexpectedly,

using the mouth as a third hand to handle tar-coated nets seemed to protect fishermen from the disease. It was not possible to attribute the higher risk to a particular work activity, nor was a specific carcinogen identified.

2896 AN EPIDEMIOLOGICAL STUDY OF BLOOD SCREENING TESTS AND ILLNESS HISTORIES AMONG CHEMICAL WORKERS INVOLVED IN THE MANUFACTURE OF POLYVINYL CHLORIDE. (Eng.) Wyatt, R. H. (Coll. Med., Univ. Kentucky, Lexington); Kotchen, J. M.; Hochstrasser, D. L.; Buchanan, J. W., Jr.; Campbell, D. R.; Slaughter, J. C.; Doll, A. H. *Ann. N.Y. Acad. Sci.* 246:80-87; 1975.

When five cases of liver angiosarcoma were identified among polyvinyl chloride manufacturing workers in a single plant, 882 male employees were screened for blood chemistry abnormalities and illness history. The results obtained from 413 of these workers, who had worked for more than one month in the manufacturing unit, were compared with the remaining workers employed in other areas. Two additional cases of angiosarcoma were discovered in the manufacturing workers through this screening. Blood samples were tested for total protein, albumin, calcium, inorganic phosphate, creatine, uric acid, total bilirubin, alkaline phosphatase, LDH, SGOT, cholesterol and creatine phosphokinase. Colorimetric analysis was performed and enzymatic reactions were read in the 340 nm range. Liver-spleen disease and allergic problems were observed more frequently in manufacturing workers than other workers while more genitourinary illness was found in the other workers. Whereas more polyvinyl chloride workers had abnormally elevated albumin levels, more workers in other areas had elevated SGOT and alkaline phosphatase levels. After adjusting for age, both albumin and cholesterol level trends with age were found to be different for the two populations. This was not found in any other test. Further study is indicated.

2897 OCCUPATIONAL RADIATION EXPOSURE DUE TO ^{222}Rn IN NATURAL GAS AND NATURAL GAS PRODUCTS. (Eng.) Gesell, T. F. (Univ. Texas Health Science Center at Houston, P.O. Box 20186, Houston, Tex. 77025) *Health Phys.* 29(5):681-687; 1975.

Nine geographically diverse natural gas processing plants were studied in an effort to quantify the potential occupational exposure from external and internal exposure to radon-222 and its daughters. Each identified input and output stream of the plants was sampled for analysis. Following analysis, an activity balance was performed for one of the plants which showed that the major pathways for radon-222 within the plant had been identified and that 97% of the radon entering the plant was accounted for. The principal result was that radon was preferentially concentrated in the ethane and propane streams and was largely removed from the methane output of the plant. Concentrations of radon-222 were determined in the streams of the remaining eight plants, but activity balances were not performed. In all cases, the highest external radiation levels were on the surface of the various product pumps. Propane reflux pumps exhibited the highest level in all but one case. No external radiation levels above 8 mR/hr were found. Measurements were made at equipment surfaces but, in all cases, the equipment was in low occupancy areas and there was no way to hypothesize a whole body exposure rate in excess of 2 mR/hr (the generally acceptable level for nonrestricted areas). It is concluded that no substantial external radiation hazard exists in the plants surveyed. Since only nine of the existing 805 plants in the U.S. were surveyed, there may be some plants with whole body radiation levels above 2 mR/hr. The potential hazard of long-lived radon-222 daughters built up on the internal surfaces of processing equipment is recognized but could not be evaluated because no equipment was encountered in the disassembled condition.

2898 CELL KINETICS METHODS FOR CLINICAL USE: ASSESSMENT OF AUTORADIOGRAPHY AND ^{125}I-IODO-DEOXYURIDINE WITH MOUSE EHRLICH TUMOUR. *(Eng.)* Jenkinson, I. S. (St. Vincent's Hosp., Sydney, Australia); Shuter, B. J.; Wright, P. N. M. *Cell Tissue Kinet.* 8(4):307-320, 1975.

Superficial Ehrlich tumors in male Quackenbush mice were used to assess how much information on cell kinetics could be obtained from the simplest autoradiography techniques and the *in situ* monitoring of ^{125}I-iododeoxyuridine (^{125}I-IUdR). These techniques were selected as being readily applicable to clinical situations. From 1-12 days after initiation, id and im tumors were labeled with ^{3}H-thymidine or ^{125}I-IUdR by the ip injection of 20 μCi or the id injection of the superficial tumors with 3-5 μCi; in some cases, the tumors were produced by ascites cells prelabeled with ^{125}I-IUdR. A hand-held scintillation counter was used for *in situ* monitoring of tumor radioactivity, and measurements were made of tumor growth and labeling indices. The tumors labeled with ^{3}H-thymidine were excised one hour later. The results indicated that the simple techniques of a single localized application of ^{3}H-thymidine followed by a single biopsy, or a single biopsy followed by *in vitro* labeling, were sufficient to assess the morphological and spatial distribution of labeling index values in the tumor. From this the cell production and loss rates were readily calculated, provided that the tumor's net growth rate was measurable or could be inferred from the tumor's classification in clinical applications. A single localized injection of ^{125}I-IUdR followed by daily monitoring for 1-2 wk was sufficient to assess the rate of cell loss. In slow growing tumors, this was very nearly equal to the cell production rate.

2899 NEOPLASMS IN CHILDREN AGED UP TO 14 YEARS IN THE PROVINCE OF WARSAW. (Pol.) Zaorska, B. (Wojewodski Osrodek Matki i Dziecka, ul. Zamieniecka 2/16, 04-158 Warszawa, Poland); Worowska-Rogowska, J. *Pediatr. Pol.* 50(1):75-82; 1975.

2900 INCIDENCE OF MALIGNANT NEOPLASMS IN GOIANIA. (Por.) Reboucas, M. A. (Faculdada de Medicina da Universidade Federal de Goiás, Brazil); Lopes, G. de M. P.; Cardoso, V. M. *Rev. Goiana Med.* 20(3/4):243-247; 1975.

2901 PRIMARY LIVER CANCER COINCIDENT WITH SCHISTOSOMIASIS JAPONICA. A STUDY OF 24 NECROPSIES. (Eng.) Nakashima, T. (Chiba Univ. Hosp., Chiba 280, Japan); Okuda*, K.; Kojiro, M.; Sakamoto, K.; Kubo, Y.; Shimokawa, Y. *Cancer* 36(4):1483-1489; 1975.

2902 EPIDEMIOLOGICAL ASPECTS OF CARCINOMA OF THE ENDOMETRIUM. (Ger.) Lau, H.-U. (Frauenklinik des Bereichs Medizin, Charite, DDR-104 Berlin, Tucholskystr. 2, East Germany); Petschelt, E.; Poehls, H.; Pollex, G.; Unger, H.-H.; Zegenhagen, V. *Zentralbl. Gynaekol.* 97(17):1025-1036; 1975.

2903 A DIETARY METHOD FOR AN EPIDEMIOLOGIC STUDY OF GASTROINTESTINAL CANCER. (Eng.) Hankin, J. H. (Sch. Public Health, 1960 East-West Road, Honolulu, Hawaii); Rhoads, G. G.; Glober, G. A. *Am. J. Clin. Nutr.* 28(9):1055-1061; 1975.

2904 LEUKOPLAKIA REVISITED. A CLINICOPATHOLOGIC STUDY 3256 ORAL LEUKOPLAKIAS. (Eng.) Waldron, C. A. (Emory Univ. Sch. Dentistry, Atlanta, Ga. 30322); Shafer, W. G. *Cancer* 36(4): 1386-1392; 1975.

2905 EPIDEMIOLOGY AND AETIOLOGY OF CANCER OF THE UTERINE CERVIX: INCLUDING THE DETECTION OF CARCINOGENIC *N*-NITROSAMINES IN THE HUMAN VAGINAL VAULT. (Eng.) Harington, J. S. (Cancer Res. Unit Natl. Cancer Assoc. South Africa, South African Inst. Medical Res., Johannesburg). *S. Afr. Med. J.* 49(12):443-446; 1975.

2906 EVALUATION OF THE ENVIRONMENTAL FACTORS IN WOMEN TREATED BECAUSE OF OVARIAN TUMORS. (Pol.) Pilawski, Z. (70-111 Szczecin, Al. Powstancow 72, Poland); Lazar, W.; Zoltowski, M.; Sieja, K. *Ginekol. Pol.* 46(1):39-47; 1975.

2907 CERVICAL NEOPLASIA IN RESIDENTS OF A LOW-INCOME HOUSING PROJECT: AN EPIDEMIOLOGIC STUDY. (Eng.) Ory, H. W. (Center Disease Control, Public Health Service, U.S. Dept. Health, Education, Welfare, Atlanta, Ga.); Jenkins, R.; Byrd, J. Y.; Jones, C. J.; Smith, J.; Tyler, C. W., Jr. *Am. J. Obstet. Gynecol.* 123(3):275-277; 1975.

2908 THE EPIDEMIOLOGY AND INTERRELATIONSHIP OF CERVICAL DYSPLASIA AND TYPE 2 HERPES-VIRUS IN A LOW-INCOME HOUSING PROJECT. (Eng.) Ory, H. W. (Center Disease Control, Public Health Service, U.S. Dept. Health, Education, Welfare, Atlanta, Ga.); Jenkins, R.; Byrd, J. Y.; Nahmias, A. J.; Tyler, C. W., Jr.; Allen, D. T.; Conger, S. B. *Am. J. Obstet. Gynecol.* 123(3):269-274; 1975.

2909 INTERPERSONAL TRANSMISSION OF EB-VIRUS INFECTION [letter to editor]. (Eng.) Chang, R. S. (Univ. of California Sch. Medicine, Davis, Calif.). *N. Engl. J. Med.* 293(9):454-455; 1975.

2910 SCREENING METHOD FOR THE DETECTION OF AFLATOXINS IN MIXED FEEDS AND OTHER AGRICULTURAL COMMODITIES WITH SUBSEQUENT CONFIRMATION AND QUANTITATIVE MEASUREMENT OF AFLATOXINS IN POSITIVE SAMPLES. (Eng.) Romer, T. R. (Ralston Purina Co., St. Louis, Mo.). *J. Assoc. Off. Anal. Chem.* 58(3):500-506; 1975.

2911 THE RADIOAUTOGRAPHIC TRANSFER FUNCTION AND ITS IMPLICATIONS FOR RADIOAUTOGRAPHIC METHODOLOGY. (Eng.) Shackney, S. E. (Natl. Cancer Inst., Bethesda, Md. 20014). *J. Natl. Cancer Inst.* 55(4):811-820; 1975.

See also:

* (Rev): 2401, 2403, 2407, 2419, 2425, 2432, 2434, 2447, 2448, 2449
* (Chem): 2522, 2523, 2559
* (Immun): 2752
* (Path): 2771, 2791

2912 HUMAN NEUROBLASTOMA IN NUDE MICE. (Eng.) Helson, L. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021); Das, S. K.; Hajdu, S. I. *Cancer Res.* 35(9):2594-2599; 1975.

For establishment of a reproducible model of human neuroblastoma, 2 to 5 million cells of established neuroblastoma cell lines (SK-N-SH, SK-N-MC) were injected sc or ip into 20 nu/nu mice of a predominantly Swiss background. Following latency periods of 8 to 21 days, tumors developed at the injection site and grew to 4-ml volumes within 3 wk. Histologically, the tumors resembled the original metastases from which the tumors were derived; however, the SK-N-SH appeared to have evidence of morphological differentiation. When compared to monolayer culture, the heterotransplanted SK-N-SH (from a metastatic tumor in a 5-yr old girl) tumor had decreased dopamine-β-hydroxylase activity and elevated cyclic adenosine 3':5'-monophosphate phosphodiesterase activity. Activity of cyclic adenosine 3':5'-monophosphate phosphodiesterase in the transplanted SK-N-MC tumor was not appreciably different from the activity in the cultured cells. This tumor line from a retroorbital metastasis from an adolescent girl contained choline acetyltransferase. Serum dopamine-β-hydroxylase levels in the mice bearing SK-N-SH tumor increased threefold. The SK-N-MC cultured cells lacked dopamine-β-hydroxylase and did not alter existing serum levels in the SK-N-MC tumor-bearing mice. ^{67}Ga injected iv was found to localize in the tumor after 24 hr. Heterotransplanted human neuroblastoma in the nude mouse can be a reproducible and informative model for tumor pharmacology, screening, radionuclides, tumor localization and imaging, and investigating morphological differentiation.

2913 DEVELOPMENT OF A 3T3-LIKE LINE FROM AN EMBRYO CULTURE OF AN INBRED STRAIN OF SYRIAN GOLDEN HAMSTER. (Eng.) Kuroki, T. (Inst. of Medical Science, Univ. of Tokyo, P. O. Takanawa, Tokyo 108, Japan); Miyashita, S. Y.; Yuasa, Y. *Cancer Res.* 35(7):1819-1825; 1975.

The establishment and properties of a 3T3-like cell line from an embryo culture of an inbred strain of Syrian hamster (APG) were studied. Under the "3T3" culture regimen (i.e., transfer every three days of an inoculum of 3 x 10^5 cells/60 mm dish) one of three cultures developed into a permanent cell line; the two others ceased to divide and died on day 88 and 104. The culture that survived overcame this critical stage and resumed active division after day 70. The cell line had properties very similar to those of the mouse 3T3 series and was named HAMS 3T3. The cells showed density-dependent inhibition of division with a saturation density of 1.0 x 10^6 to 1.2 x 10^6 cells/60-mm dish or 1.0 x 10^6 to 5.5 x 10^4 cells/cm^2. Addition of fresh medium containing 5 or 10% fetal calf serum to a confluent culture induced DNA synthesis in 18 hr with subsequent cell division. Cells were hyperdiploid with a mode of 45 chromosomes (80% of the cells). When cells at the 60th passage were injected into the skin or cheek pouch of an inbred hamster of the same strain as that from which they were derived, they produced a benign tumor that regressed after three weeks. When exponentially growing cells were infected with the Moloney strain of murine sarcoma virus, a change in morphology occurred about four days after infection. Cells became spindle-shaped and refractile, and grew in a criss-cross fashion forming a multilayer; this was in contrast to the confluent monolayer formed by controls. These results indicate that hamster embryo cells develop into a permanent cell line by chance, with an incidence of roughly 10-30%; this incidence varies according to culture conditions.

2914 STUDIES ON THE HUMORAL REGULATION OF GRANULOPOIESIS IN LEUKAEMIC RFM MICE. (Eng.) Gordon, M. Y. (Inst. Cancer Res., Belmont, Sutton, Surrey, England); Lindop, P. J. *Br. J. Cancer* 32 (2):186-192; 1975.

Intraperitoneal diffusion chambers were used to investigate changes in humoral factors during the development of myeloid leukemia in RFM mice. Normal mouse bone marrow cells form colonies of granulocytes and macrophages when cultured in semi-solid agar medium within intraperitoneal diffusion chambers. The use of mice bearing transplanted myeloid leukemia as agar diffusion chamber (ADC) hosts enhanced colony formation from normal marrow. The humoral basis for this stimulation was shown by the colony stimulating activity of the fluid entering the diffusion chambers when assayed against normal mouse bone marrow cells in agar culture *in vitro*. The stimulus to colony growth in ADCs and the *in vitro* colony stimulating activity depended on the phase in the development of the leukemia investigated, and the stimulation was abolished by splenectomy. There was no apparent relationship between the growth of the leukemic cell population *in vivo* and the level of the stimulating factor detected in leukemic mice. The results show that the combined effects of factors that inhibit or stimulate granulopoiesis change radically during the development of transplantable leukemia in RFM mice. These data may be compared with the increased colony stimulating factor levels associated with leukemia in man, although evidence of an early phase characterized by low levels of stimulation has not been among preleukemia patients.

2915 GRANULOPOIETIC PROGENITORS IN SUSPENSION CULTURE: A COMPARISON OF STIMULATORY CELLS AND CONDITIONED MEDIA. (Eng.) Niho, Y. (Ontario Cancer Inst., Toronto, Canada); Till, J. E.; McCulloch, E. A. *Blood* 45(6):811-821; 1975.

Kinetic studies were carried out to investigate the functional heterogeneity in populations of human marrow or peripheral blood cells separated by velocity sedimentation. Peripheral blood was obtained from seven normal volunteers and a patient with hemochromatosis; marrow was obtained from 18 patients with cancer or anemia. Cultures of these cells were assayed for granulopoietic progenitor cells and factors, or for cells that stimulate colony formation. The slowly-sedimenting cells were found to stimulate both

colony formation by granulopoietic progenitors and an increase in numbers of granulopoietic progenitors in suspension culture, while rapidly-sedimenting cell stimulated only colony formation and not increased progenitors in suspension cultures. Investigations of the properties of media conditioned by these two subpopulations of cells revealed no clear differences between them; both stimulated suspension cultures as well as colony formation, and both lost the former activity, but not the latter, after dialysis. The results evidence that more than one process is regulated in cultures of granulopoietic progenitor cells.

2916 THE EFFECTS OF TOPOINHIBITION AND CYTOCHALASIN B ON METABOLIC COOPERATION. (Eng.) Stoker, M. (Imperial Cancer Res. Fund Laboratories, Lincoln's Inn Fields, London WC2, England). *Cell* 6(2):253-257; 1975.

The effects of topoinhibition, topostimulation, and cytochalasin B on metabolic cooperation (the ability to form intercellular junctions) of 3T3 cells were examined in a stationary monolayer culture. A line of polyoma-transformed BHK cells (TG1) lacking hypoxanthine guanine phosphoribosyl transferase was used as an indicator. TG1 cells incorporated [^{3}H]hypoxanthine into nucleic acids when in prolonged (20 hr) or brief (1 hr) contact with donor 3T3 cells, whether the 3T3 cells were in a quiescent layer or in the region of stimulation at the edge of the wound. Cytochalasin B (1 μg/ml) prevented the development of metabolic cooperation between donor 3T3 cells and recipient BHK cells and abolished most pre-existing cooperation. Metabolic cooperation resumed three hours after the removal of cytochalasin B. The proportion of residual cooperating cells at different doses of the drug remained unaffected by the position in the edge or in the layer, and was not correlated with topostimulation. The results support the hypothesis that alterations in the capacity to form stable intercellular junctions is not a necessary feature of the topoinhibition phenomenon.

2917 OCCLUDING JUNCTIONS AND CELL BEHAVIOR IN PRIMARY CULTURES OF NORMAL AND NEOPLASTIC MAMMARY GLAND CELLS. (Eng.) Pickett, P. B. (Dept. Zool., Univ. California, Berkeley); Pitelka, D. R.; Hamamoto, S. T.; Misfeldt, D. S. *J. Cell Biol.* 66(2):316-332; 1975.

Dome-forming primary cultures of cells dissociated from normal prelactating mouse mammary glands or from spontaneous mammary adenocarcinomas were examined with particular attention to morphological polarity and cell junctions to determine to what extent cultured cells resemble mammary epithelium in structural organization. Spontaneous mammary tumors from BALB/cfC3H/Crgl or from C3H/Crgl multiparous mice and normal mammary glands from 14- to 19-day pregnant females of the same strains or BALB/cCrgl were minced and dissociated. The cell suspension was washed, filtered and plated at high density (5×10^{-5} cells/cm^2 of substrate). Tumorigenicity of cultured cells was tested by sc injection into isogenic mice of 10^5 cells from 14-day-old primary normal and tumor cultures. Tumors developed from all of six tumor cell implants and from neither of two normal cell implants. The cultures were examined microscopically alive and in thick and thin sections and freeze-fracture replicas. Pavement cells in all cases were polarized toward the bulk medium as a lumen equivalent, with microvilli and continuous, well-developed occluding junctions at this surface. Between the pavement and the substrate were other cells, of parenchymal or stromal origin, scattered or in loose piles; these sequestered cells were relatively unpolarized and never possessed occluding junctions. Small gap junctions were seen in the pavement layer, and desmosomes could be seen linking epithelial cells in any location. Development of the epithelial secretory apparatus was not demonstrable under the culture conditions used; normal and neoplstic cells did not differ consistently in any property examined. The roof of a dome was merely a raised part of the epithelial pavement and did not differ from the latter in either cell or junction structure. Dome formation may demonstrate the persistance of some transport functions and of the capacity to form effective occluding junctions. These basic epithelial properties may survive both neoplastic transformation and transition to culture.

2918 THE CONTROL OF ANAEROBIC GLYCOLYSIS BY GLUCOSE TRANSPORT AND OUABAIN IN SLICES OF HEPATOMA 3924A. (Eng.) Van Rossum, G. D. V. (Temple Univ. Sch. Med., Philadelphia, Pa. 19140); Galeotti, T.; Palombini, G.; Morris, H. P. *Biochim. Biophys. Acta* 394(2):267-280; 1975.

The activities of glycolysis and K^+ transport were studied in slices of Morris hepatoma 3924A incubated under anerobic conditions in the presence of glucose at 1-50 mM. The tumors were grown for 20-25 days in ACI/T rats. Ouabain-sensitive net transport of K^+ was observed at all glucose concentrations greater than 1 mM; ouabain reduced the rate of glycolysis by about 25% at all glucose concentrations able to support ion transport. The net entry of glucose into the intracellular phase was studied at varying glucose concentrations. The rate of net entry of glucose was similar to the rate of glucose utilization by anerobic glycolysis at concentrations of 10 mM and less, but exceeded the rate of glycolysis at 20 mM and above. The glucose entry was not Na^+-dependent and was not inhibited by ouabain. The results suggest that the reduction in glycolytic activity caused by ouabain is not due to an inhibition of glucose transport and that the glucose transport system of this hepatoma has properties similar to that of normal liver.

2919 THE EFFECT OF FLAVONOIDS ON AEROBIC GLYCOLYSIS AND GROWTH OF TUMOR CELLS. (Eng.) Suolinna, E. M. (Section of Biochemistry, Molecular and Cell Biology, Cornell Univ., Ithaca, N.Y. 14853); Buchsbaum, R. N.; Racker, E. *Cancer Res.* 35(7):1865-1872; 1975.

The effects of bioflavonoids on the aerobic glycolysis

f several tumor cell lines (Ehrlich ascites cells, ells from DBA mice with L1210 and P388 leukemia, and at myeloblasts transformed with Kirsten mouse sar- oma virus) as well as on mitochondria and plasma embrane ATPase were studied. The effect of quer- etin on the growth of these cells and on baby ham- ter kidney cells in culture was also studied. etra- and pentahydroxy flavones with hydroxyl groups t 3, 3', 4', 5 and 7 (*e.g.*, quercetin) were the most ctive. They inhibited the activity of isolated Na^+-K^+-ATPase of the plasma membrane and of mitochondrial denosinetriphosphatase, but under appropriate con- itions did not interfere with the ion transport ac- ivity of the ATPases. Therefore, they increased the ranslocation efficiency of the ion pump. In several umor cells, loosely coupled ion pumps were respon- sible for the high rate of aerobic glycolysis. In such cells, addition of quercetin induced the cells o pump ions with greater efficiency. Quercetin also caused pronounced inhibition of growth at 5-20 μg/ml of growth medium in both normal and transformed cells. It is proposed that these flavones may act similarly to the natural regulatory components that inhibit ATP hydrolysis without impairing the energy-transducing system that generates ATP. The flavones may serve as useful tools in the analysis of the control of syn- thesis of macromolecules.

2920 INTRACELLULAR cAMP LEVELS IN NORMAL RAT MAMMARY GLAND AND ADENOCARCINOMA. *IN VIVO* vs *IN VITRO*. (Eng.) Cohen, L. A. (Naylor Dana Inst. Dis. Prev., New York, N.Y.) Chan, P. C. *Life Sci.* 16(1):107-115; 1975.

Mammary adenocarcinomas were induced in Sprague-Dawley rats by po administration of 10 mg of 7, 12 dimethylbenz[a]anthracene. The intracellular cyclic AMP levels in these tumors were determined *in vivo* and in monolayer cultures derived from the tumors by radioimmunoassay. It was found that levels were higher in mammary tumors (0.643 pM/mg wet wt) than in normal gland (0.158 pM/mg). In contrast, cyclic AMP levels in cultured adenocarcinoma cells were lower at day 10 (13 pM/mg protein) than those in normal mammary epithelial cells (32 pM/mg protein). The apparent contradiction may be a consequence of the fact that *in vivo* cyclic AMP values represent the average value of the composite cell types and not the epithelial components in question.

2921 EFFECTS OF CARBARYL AND DIELDRIN ON THE GROWTH, PROTEIN CONTENT, AND PHOSPHOLIPID CONTENT OF HeLa CELLS. (Eng.) Blevins, R. D. (East Tennessee State Univ., Johnson City); Dunn, W. C., Jr. *J. Agric. Food Chem.* 23(3):377-382; 1975.

Monolayer cultures of HeLa cells were used to monitor the effects of two insecticides on cell numbers, protein content, and phospholipid content. HeLa cells were incubated for 48 hr with 1, 2, 4, or 8 ppm carbaryl and dieldrin (analytical grade). Both compounds stimulated cell division at 1 and 2 ppm and inhibited growth at 4 and 8 ppm. Carbaryl was more toxic than dieldrin at 4 and 8 ppm. A decrease in cellular protein was noted with carbaryl at 4 ppm and with dieldrin at both concentrations. Increasing concentrations of carbaryl caused subsequent increases in sphingomyelin content of the phospholipid fractions of exposed cells suggesting inhibition of sphingomyelinase. Both carbaryl and dieldrin elicited decreases in the amounts of phosphatidylcholine, and a slight increase in lysophosphatidylcholine was noted in cells exposed to carbaryl. The results indicate that insecticides from different chemical groups are nonspecific in their action upon mammalian cells *in vitro*. The variations in phospholipid content of HeLa cells caused by carbaryl and dieldrin suggest an alteration of the structure of cellular membranes.

2922 REGULATION OF PROTEIN SYNTHESIS AT THE TRANSLATIONAL LEVEL IN NEUROBLASTOMA CELLS. (Eng.) Zucco, F. (C.N.R., Laboratory of Molecular Embryology, 80072 Arco Felice, Naples, Italy); Persico, M.; Felsani, A.; Metafora, S.; Augusti-Tocco, G. *Proc. Natl. Acad. Sci. USA* 72(6):2289-2293; 1975.

In vitro protein synthesis in neuroblastoma cells placed in two different growth conditions was studied. Neuroblastoma clone $41A_3$ was grown in monolayer and suspension culture. Assays of standard cell-free protein synthesis, total soluble activity, and total transfer activity were performed. Polysome sucrose density gradient analysis and acrylamide gel electrophoresis were also performed. The specific activity of the lysate increased during growth of the monolayer cultures, yet showed little change in the suspension cultures. Both the rate and extent of protein synthesis were markedly higher in the lysate from monolayer cells. The specific activity of monolayer cell sap was twice as high as that of suspension. Although the activities of elongation factors I and II and of aminoacyl-transfer RNA synthetases were the same in both cell saps, the suspension cells were two times more active in elongating polypeptide chains. Ribosome activity was found to be two times higher in the monolayer cells, as was the polysomes/monosomes ratio. Although the total ribosomal population in monolayer cells was about twice that present in suspension cells, there was no significant change in the polysome size among the two cell types. Cross experiments suggested that both ribosomes and some of the soluble factors were involved in determining the higher activity of the monolayer lysate. The overall patterns of the proteins released from reconstituted cell-free systems were similar, but quantitative differences were noted. The data indicate that the transition of neuroblastoma cells from suspension to monolayer growth conditions involve a marked increase in the protein-synthesizing activity.

2923 PROPERTIES OF CHROMOSOMAL PROTEINS OF HUMAN LEUKEMIC CELLS. (Eng.) Desai, L. S. (Harvard Medical Sch., Boston, Mass. 02115); Wulff, U. C.; Foley, G. E. *Biochimie (Paris)* 57(3):315-323; 1975.

Purified chromatin isolated from lymphocytic cells derived from patients with infectious mononucleosis (lines CCRF-RKB and CCRF-SB) or acute lymphoblastic

leukemia (lines CCRF-H-SB and CCRF-CEM) was compared with chromatin isolated from normal human lymphocytic cells (lines CCRF-SLT and CCRF-TOH) by gel electrophoresis and differential gradient ultracentrifugation. Thermal denaturation studies showed higher melting temperature values for chromatin from leukemic cells (84.7 and 84.3 for lines CCRF-H-SB and CCRF-CEM, respectively) as compared to that of lymphocytic cells from normal donors (76.8 and 77.1 for CCRF-SLT and CCRF-TOH, respectively) from patients with infectious mononucleosis (81.4 and 82.2 for CCRF-RKB and CCRF-SB, respectively). This reflects the diverse complexity of these chromatins with respect to their varying chemical compositions. There were significant differences in the ratios of DNA:RNA:protein, as well as in the ratios of chromatin-associated histone and nonhistone proteins; although chromatin-associated histones were more homogeneous than were the nonhistone proteins, as judged by amino acid analyses and acrylamide gel electrophoresis. These differences in chromatin structure may relate to the differences in gene expression characteristic of these lymphocytic cells. The chromosomal acidic proteins isolated from the purified chromatin of human leukemic cells greatly stimulated the template activity of the chromatin in *in vitro* RNA synthesis. The nonhistone proteins selectively interact with chromatins and influence the RNA polymerase reactions, indicating that there is selective tissue specificity of nonhistone proteins. These proteins may play a greater role in transcription mechanisms and are more loosely bound to chromatins than to histones.

2924 SULFHYDRYL GROUP QUANTITATION OF HEPATOMA AND LIVER MICROSOMAL FRACTIONS. (Eng.) Stratman, F. W. (Inst. Enzyme Res., Univ. Wisconsin, Madison); Hochberg, A. A.; Zahlten, R. N.; Morris, H. P. *Cancer Res.* 35(6):1476-1484; 1975.

The relationship of sulfhydryl and disulfide groups to protein synthesis in normal and rapidly growing tissues was investigated by quantitation of sulfhydryl groups in endoplasmic reticulum and polyribosomes of livers from fed or 24-hr-fasterd Sprague-Dawley rats, normal Buffalo rats, or rats with Morris hepatoma. Stripping the smooth endoplasmic reticulum of normal liver with potassium chloride and EDTA reduced the sulfhydryl groups available for carboxamide methylation by iodoacetamide by 15%, while stripping the rough endoplasmic reticulum increased the available groups by 30%. This could reflect the removal of ribosomes from rough endoplasmic reticulum with the subsequent exposure of sulfhydryl groups. Exposed sulfhydryl groups of normal mature female rat liver smooth endoplasmic reticulum were decreased to a similar degree by the stripping procedure with EDTA and potassium chloride when quantitated by either iodoacetamide or 4,4'-dithiodipyridine. In immature male and female rats, however, the stripping procedure failed to decrease the exposed sulfhydryl groups of smooth endoplasmic reticulum. Stripping rough endoplasmic reticulum from the livers of mature and immature rats and using iodoacetamide showed an increased quantity of exposed sulfhydryl groups, but using 4,4'-dithiodipyridine resulted in no change. The negative correlation between exposed sulfhydryl groups in the polyribosomes and the rate of growth of normal liver and of Morris hepatomas 6 and 38B suggests that the conformation of the free polyribosomal proteins could be a control factor for the rate of protein synthesis. Faster growing hepatomas also have greater quantities of sulfhydryls and disulfides.

2925 LOCALIZATION AND PHOSPHORYLATION OF NUCLEAR, NUCLEOLAR AND EXTRANUCLEOLAR NON-HISTONE PROTEINS OF NOVIKOFF HEPATOMA ASCITES CELLS. (Eng.) Olson, M. O. J. (Baylor Coll. Medicine, Houston, Tex. 77025); Ezrailson, E. G.; Guetzow, K.; Busch, H. *J. Mol. Biol.* 97(4):611-619; 1975.

Novikoff hepatoma ascites cells were studied to determine whether any non-histone proteins are localized in either the nucleolar or extranucleolar chromatin fraction, and whether any of the proteins in either fraction were specifically labeled with ^{32}P. Rats (male, Holtzman) bearing ascites cells were injected ip with 20 mCi of carrier-free [^{32}P]orthophosphate 2 hr before sacrifice. Chromatin was prepared from whole nuclei, nucleolar and extranucleolar fractions. After removal of histones by 0.4-NH_2SO_4 and digestion of the DNA by DNase I, the nonhistone proteins were subjected to two-dimensional electrophoresis and autoradiography. Although most non-histone proteins were common to both fractions, the nucleolar fraction was enriched in proteins C18, C21, Cg' and CB. Proteins CM, C6, CA, Cb, B24, B22 and BF were found in higher concentrations in the extranucleolar component. In the nucleolar fraction, only protein C18 was labeled significantly with ^{32}P. In the extranucleolar fraction, ^{32}P was incorporated into protein spots C18, Cg', CM, CN and C6. Analyses of ^{32}P-labeled spots for phosphoamino acids indicated that all spots analyzed contained ^{32}P-labeled phosphoserine. The results indicate that nucleolar chromatin contains specific proteins which have a unique ^{32}P labeling pattern.

2926 IDENTIFICATION OF A HIGH MOLECULAR WEIGHT TRANS-MEMBRANE PROTEIN IN MOUSE L CELLS. (Eng.) Hunt, R. C. (Univ. Virginia Sch. Medicine, Charlottesville, Va. 22901); Brown, J. C. *J. Mol. Biol.* 97(4):413-422; 1975.

A new method for the identification of "trans-membrane" proteins in cultured animal cells is described. Proteins exposed on the outer cell surface are labeled with ^{125}I by the lactoperoxidase technique. "Inside-out" membrane vesicles are prepared from the labeled cells using the polystyrene latex bead procedure. These inside-out vesicles are then treated briefly with trypsin and analyzed for the presence of ^{125}I-labeled protein species which were degraded by proteolytic attack. Such proteins must be exposed on both the outer and inner membrane surfaces and, therefore, they must pass through the lipid barrier. The method showed a particular high molecular wt polypeptide chain spans the plasma membrane of mouse L cells. It is similar in its iodinatability and molecular wt to a protein recently found on the surface of normal, but not virus-transformed fi-

oroblasts. The method is most suitable for cultured cells, and requires that the cells can ingest polystyrene latex beads by endocytosis.

2927 PRODUCTION OF FERRITIN BY RAT HEPATOMA CELLS *IN VITRO*: DEMONSTRATION OF PROTEIN SUBUNITS AND FERRITIN BY IMMUNOFLUORESCENCE. (Eng.) Lee, J. C. K. (Univ. Rochester Sch. Medicine and Dentistry, Rochester, N.Y. 14642); Lee, S. S. C.; Schlesinger, K. J.; Richter, G. W. *Am. J. Pathol.* 80(2):235-248; 1975.

Using precipitating antibodies to ACI rat liver ferritin and to sodium-dodecyl-sulfate-dissociated protein subunits of ACI rat liver ferritin, the presence of ferritin-positive sites and subunit-positive sites *in situ* was demonstrated in several rat hepatoma cell lines by immunofluorescence. Hepatoma cells from three transplantable rat hepatomas (Reuber H-139, Reuber H-35, and Morris 5123) were explanted and propagated. Rabbit antibodies specific for either protein subunits of ferritin or ferritin were prepared by affinity chromatography or by dissociation of antibody-antigen complexes with 0.1 M acetic acid followed by differential ultracentrifugation. Explants of Reuber H-139, Reuber H-35, and Morris 5123 hepatoma cells, grown either in ordinary McCoy's 5a medium or in such medium enriched with iron (0.002% Fe), gave positive immunofluorescence for subunits as well as ferritin. Exposure of a clonal strain of Morris 5123 hepatoma cells to iron-enriched culture medium for varying lengths of time of up to 24 hr resulted in progressive increase in the quantity of ferritin-specific immunofluorescent cytoplasmic material, which was at first present diffusely, and later in clumps. By contrast, during the initial 24-hr period, subunit-specific immunofluorescence remained at relatively low intensity, with diffuse distribution through the cytoplasm. These findings indicate a) the presence, in the cytoplasm, of the three kinds of hepatoma cells, of unassembled or only partly assembled subunits or fragments of subunits as well as of ferritin, and b) rapid assembly of the protein subunits into apoferritin and ferritin after administration of iron, so that the concentration of subunits in the cytoplasm was not significantly increased.

2928 CHARACTERIZATION AND SUBUNIT ANALYSIS OF FERRITIN ISOLATED FROM NORMAL AND MALIGNANT HUMAN LIVER. (Eng.) Alpert, E. (Harvard Med. Sch., Boston, Mass.). *Cancer Res.* 35(6):1505-1509; 1975.

An attempt was made to characterize the molecular basis for the previous finding of isoferritin variants (carcinofetal isoferritins) in liver carcinoma and fetal liver. Ferritin was purified from normal, fetal and malignant liver tissue obtained at autopsy. Ferritin from hepatoma tissue migrated faster than normal human liver ferritin in gel electrophoresis and had its major peaks focusing at a more acidic pH than normal. Hepatoma and fetal liver ferritin contained an acidic component in gel and liquid isoelectric focusing not found in normal liver ferritin. Comparisons of ferritins purified from human liver cell carcinoma and normal liver showed that both ferritins consisted of a subunit species with an identical molecular weight of approximately 18,500. Two subunits were demonstrable in normal liver ferritin by means of acrylamide electrophoresis and 8 M urea in acid pH. The same two subunits were also demonstrable in ferritin isolated from human liver cell carcinoma along with a third subunit, intermediate in charge between the two normal liver subunits. This was demonstrable in different amounts in ferritins from two hepatomas. The isolated acidic isoferritin was immunologically identical to normal liver isoferritins. It is concluded that the multiple isoferritins of the human liver ferritin consist of two subunits, which are identical in molecular weight but which differ in net charge. Ferritin, isolated from two human liver carcinoma tissues, was composed of the same two subunits and a third unique subunit. Different amounts of these subunits may account for the several normal isoferritins and a unique tumor-specific acid isoferritin found in hepatoma.

2929 DNA SYNTHESIS IN TUMOR-BEARING RATS. (Eng.) Shirasaka, T. (Sch. Med., Tokushima Univ., Japan); Fujii, S. *Cancer Res.* 35(3):517-520; 1975.

The synthesis of DNA in tumor-bearing male Donryu rats was studied. Yoshida sarcoma and AH130 cells were transplanted ip. After five days, 5×10^7 ascites cells were transplanted subepidermally on the back of rats, to produce solid tumors of each type. Rats bearing either tumor were killed and their liver, spleen, and tumor tissues were used for DNA and enzyme assays. Solid tumor was used 1 or 2 wk after transplantation. Partial hepatectomy was performed on some rats, and the regenerated tissue was removed 48 hr after hepatectomy. Incorporation of tritiated thymidine (TdR) into DNA was measured and the activities of TdR kinase, thymidine monophosphate (TMP) kinase and DNA polymerase were also assessed. In the partially hepatectomized rats, TdR incorporation into DNA was increased in the liver but not in the spleen; however, the activities of TdR and TMP kinases and DNA polymerase were increased in liver and in spleen. High activities of these enzymes were also found in both Yoshida sarcoma and AH130 tumors, and TdR incorporation was also increased. Elevated levels of these enzymes were also found in the liver and spleen of animals bearing both cell types. Activity of the enzymes was shown to rise at the fourth day after transplantation in the liver of rats bearing Yoshida sarcoma. However, in the sera of these animals, only TdR kinase and DNA polymerase increased after four days. TdR incorporation and TMP kinase were not detectable in the sera of these animals. Diethylaminoethyl-cellulose column chromatography showed the serum TdR kinase of Yoshida sarcoma-bearing rats to consist of two fractions while liver TdR kinase had only one fraction that was identical to one of the serum fractions. Serum TdR kinase activity was shown to decrease after the removal of the tumor. It is suggested that the serum TdR kinase is derived from the Yoshida sarcoma, while that of the liver is derived from *de novo* synthesis and may be enhanced by some tumor substance.

2930 CORRELATION BETWEEN DNA SYNTHESIS AND INTRACELLULAR NAD IN CULTURED HUMAN LEUKEMIC LYMPHOCYTES. (Eng.) Chang, S. C. S. (Lab. Mol. Biol., Mayo Found., Rochester, Minn.); Bernofsky, C. *Biochem. Biophys. Res. Commun.* 64(2):539-545; 1975.

The relationship between DNA synthesis and intracellular nicotinamide (NAD^+) was examined in lymphocytes from an individual with acute monocytic leukemia, which were adapted to tissue culture. The nicotinamide concentration of the culture medium was 7.0 μM. The cells were maintained at a concentration of 2-4 x 10^6 cells/ml. The NAD^+ level of the freshly-isolated leukemia lymphocytes was 67 nM/10^9 cells (56 nM /10^9 cells normal). The NAD^+ content of the acute monocytic leukemia cells increased steadily and reached a final level of about 350 nM/10^9 cells at about the time the cells became established (four wk). When the NAD^+ level of established cells was lowered by means of a nicotinamide-poor medium or by the action of 1-methyl-1-nitrosourea, there was a concomitant decrease in the rate of DNA synthesis. Upon incubation of the leukemic lymphocytes with 4 nM 1-methyl-1-nitrosourea, the NAD^+ level decreased rapidly, reaching 50% of its initial value in 24 min. Measurement of [^{3}H]thymidine incorporation into DNA showed that the rate of DNA synthesis in 1-methyl-1-nitrosourea-treated cells immediately decreased to 7% of the rate in untreated cells. When established cells were transferred to a nicotinamide-poor medium, the level of NAD^+ and the rate of DNA synthesis decreased in a parallel fashion, and after four days were 61% and 47% of their initial values, respectively. Cells treated comparably but with complete medium maintained a NAD^+ level of 307 nM/10^9 cells and incorporated [^{3}H]thymidine at a mean rate of 16.8 x 10^4 cpm. These results indicate that there is a direct relationship between the level of NAD^+ and the rate of DNA synthesis.

2931 ON THE CHARACTER OF THE NUCLEAR MEMBRANE-ASSOCIATED DNA OF HELA CELLS. (Eng.) Cabradilla, C. D. (Hazelton Lab., 9200 Leeberg Pike, Vienna, Va. 22180); Toliver, A. P. *Physiol. Chem. Phys.* 7(2):153-166; 1975.

The nature of DNA-membrane complexes isolated from synchronized HeLa cells was studied. Monolayer cultures of HeLa cells, strain S_3, were used throughout the study. 5-Fluorodeoxyuridine was used as the synchronizing agent. DNA isolated from either nuclei or nuclear membranes by the chloroform:isoamyl alcohol method was analyzed in either neutral or alkaline CsCl equilibrium density gradients. Although most of the DNA synthesis occurring in the nucleoplasm appeared to be the result of repair replication, virtually all of the membrane-associated DNA appeared to be the result of semiconservative replication. Hydroxylapatite column chromatography suggested that the nascent DNA associated with the membrane may exist as a nicked duplex; also, 14-15% eluted as single-stranded DNA. Buoyant density studies and the thermal melting profile suggested a guanine-cytosine base content of 40%, and indicated that the base content of the membrane-associated and bulk DNA were identical. Stability studies revealed sensitivity (release) of the membrane-DNA to DNase I, proteolytic enzymes, NaCl, and deoxycholate and phospholipase C. The results of treating nuclear membranes isolated on sucrose-shelf gradients with such agents suggested that the DNA is associated with a lipoprotein structure.

2932 DNA FROM EUKARYOTIC CELLS CONTAINS UNUSUALLY LONG PYRIMIDINE SEQUENCES. (Eng.) Birnboim, H. C. (Biology and Health Physics Div., Atomic Energy Canada Ltd., Chalk River, Ontario, Canada); Straus, N. A. *Can. J. Biochem.* 53(5):640-643; 1975.

The presence of polypyrimidines in DNA from several different higher organisms was investigated. Samples of [^{3}H]thymidine-labeled DNA were subjected to acid hydrolysis and gel electrophoresis; nucleosides were separated by paper chromatography. In quantitating polypyrimidines *via* formic acid-diphenylamine hydrolysis of the samples, long pyrimidine tracts were separated by ethanol precipitation followed by polyacrylamide gel electrophoresis. Duplicate analyses of a single sample of L-cell DNA resulted in values agreeing within 10-30%. The highest content of polypyrimidines was found in mouse L-cell DNA (0.8%). Human HeLa cells, rabbit cells, and Chinese hamster cells had about one half the amount (0.3-0.5%). Small amounts of polypyrimidines were also found in xenopus and bovine DNA (0.07-0.08%), and lesser amounts were detected in adenovirus type 12, polyoma, and *Escherichia coli* DNA (0.025, 0.023, and 0.009%, respectively). It is unlikely that such polypyrimidines arose from culture contaminants. Thus, the data indicate that polypyrimidines are not unique to human DNA, but are found in DNA from several different organisms. This suggests that polypyrimidines represent a relatively old evolutionary component, possibly with a chromosomal or regulatory function.

2933 IS FANCONI'S ANAEMIA DEFECTIVE IN A PROCESS ESSENTIAL TO THE REPAIR OF DNA CROSS LINKS? (Eng.) Sasaki, M. S. (Tokyo Medical and Dental Univ., Yushima, Tokyo 113, Japan). *Nature* 257(5527):501-503; 1975.

The hypothesis that lymphocytes from patients with Fanconi's anemia (FA) are defective in DNA repair was tested by determining the chromosome response of lymphocytes from two male FA patients (aged 6 and 7 yr) to mitomycins in relation to the cell cycle phase at time of treatment. At various times before fixation, FA cells were treated for 30 min with difunctional mitomycin C (MMC, 0.1 μg/ml) or monofunctional decarbamoyl mitomycin C (DCMMC, 50 μg/ml) in medium containing [^{3}H]thymidine. After a corresponding recovery time in medium free of test compounds, the chromosome preparations were processed for autoradiography and analyzed for both their metaphase labeling pattern and for the presence of chromosome aberrations in labeled and unlabeled mitoses. Treatment with mitomycins reduced the rate of progression through the cell cycle; the effect was more marked in cells treated with MMC. Both DCMMC and MMC induced significant chromosome aber-

rations of the chromatid type. The patterns of the chromosome response of normal control cells to DCMMC and MMC, and of FA cells to DCMMC, were as predicted for repair-proficient cells. The S phase was the most sensitive stage with respect to formation of chromosome aberrations. The aberrations were less frequent in unlabeled mitoses in the pre-DNA synthesis stage at time of treatment. Their frequencies varied with recovery time, being maximum in late G_1, and decreasing with increasing recovery time. FA cells treated with MMC were most sensitive at G_1 and yielded a constant rate of aberrations when treated in various parts of G_1. The yield decreased as the S phase progressed. These results indicate that pre-aberration lesions induced in FA cells by DCMMC can be repaired; those induced by MMC at any time before DNA synthesis are not repaired and link maximally to the chromosome aberrations formed during the subsequent S phase. FA cells are also abnormally susceptible to chromosome breakage by the psoralen-plus-light reaction, which is highly specific to native DNA and induced interstrand cross links. Thus, the irreparable MMC-induced lesions in FA cells are probably DNA cross links of the interstrand type.

2934 DNA MEASUREMENTS ON CELL NUCLEI OF NORMAL, PROLIFERATING AND NEOPLASTIC THYROID TISSUES IN RATS. (Eng.) Christov, K. (Acad. Medicine, Sofia-56, Bulgaria); Thomas, C.; Sandritter, W. *Neoplasma* 22(3):285-294; 1975.

Nuclear DNA content was measured in three normal, nine hyperplastic and 16 neoplastic rat thyroid glands. Thyroid hyperplasia and tumor growth were induced six months after treatment of 10-day-old male Wistar rats with both X-rays (300 rads) and methylthiouracil (0.1% in drinking water). In the untreated control animals, only diploid thyroid epithelial cells were observed. At the stages of diffuse and nodular thyroid hyperplasia, the total DNA content per nucleus indicated a diploid chromosome number, and only a few cells were hyperdiploid. In the thyroid adenomas and carcinomas, a scattering of the diploid region and an increase in the number of hyperdiploid cells was found. Among the various types of thyroid tumors neither difference in the number of hyperdiploid cells, nor typical pattern of distribution of these cells in the histogram was found. The increased number of hyperdiploid cells in the hyperplastic and neoplastic thyroids suggest an increase in the proportion of the cells entering the cell cycle, and does not indicate the appearance of a neoplastic stemline.

2935 NUCLEAR PENETRATION AND STIMULATION OF NUCLEIC ACIDS SYNTHESIS BY POLY(A)-POLY(U) IN MAMMALIAN CELLS. (Eng.) Fenster, E. D. (Institut Gustave-Roussy, Groupe de Recherche No. 8 du CNRS, Villejuif F-94800, France); Lacour, F.; Harel, J. *Exp. Cell Res.* 94(2):315-320; 1975.

The uptake of poly(A)-poly(U) in cultured normal human lymphocytes (LHN13) or in mouse ascites tumor cells (FLS) was studied. The rapid penetration of poly(A)-poly(U) into cell nuclei was demonstrated by autoradiography, by recovery of acid-precipitable material from isolated nuclei, and by sucrose gradient centrifugation of nuclear lysates. The majority of poly(A)-poly(U) remained intact in the nuclei for at least 2½ hr. This penetration increased 20-fold by pretreatment of the cells with DEAE Dextran. In cells treated with DEAE Dextran. DNA and RNA syntheses stimulated by poly(A)-poly(U) from the time the polymer complex was added to at least 2½ hr. The authors postulate that this early increased nucleic acid synthesis might be related to immune stimulation by poly(A)-poly(U).

2936 POLY ADENYLIC ACID SYNTHESIS *IN VITRO* IN ISOLATED HeLa CELL NUCLEI AND WHOLE CELL HOMOGENATES. (Eng.) Jelinek, W. R. (Dep. Biol. Sci., Columbia Univ., New York, N.Y.). *Cell* 2(3): 197-204; 1975.

The possibility that HeLa cell nuclei could synthesize poly(A) similar to that found in growing cells, and whether *in vitro*-synthesized poly(A) was part of heterogeneous nuclear RNA were studied in cell-free homogenates. Synthesis of poly(A) by isolated nuclei did not occur at low [^{3}H]ATP concentrations as demonstrated on poly(U)-sepharose column affinity chromatography. Nuclei from 2 x 10^7 to 3 x 10^7 cells were purified and resuspended in 1 ml of the cytoplasmic supernatant from the original cell homogenate, 0.1 mM each guanosine triphosphate and cytosine triphosphate, and 50 μCi [^{3}H]uridine. After 20 min incubation at 37 C, RNA was obtained by phenol extraction and poly(A)-containing molecules were selected by chromatography. When ATP concentration in the medium was increased to 0.10 or 0.20 mM, the total AMP incorporated into poly(A) was stimulated 180- to 660-fold, respectively, whereas total RNA synthesis as measured by total AMP incorporated was increased only 2.5-3.5 times. In the presence of cytoplasmic extract, total RNA synthesis was stimulated about 10-fold over that when a concentration of ATP equal to that found in cytoplasm was present. Poly(A) synthesized in both purified nuclei and in whole cell homogenates was identical to that synthesized *in vivo*. When undigested with T1 and pancreatic ribonuclease, bound molecules of *in vitro*-synthesized RNA contained poly(A) the size of *in vivo*-synthesized, poly(A)-containing heterogeneous nuclear RNA. Polyacrylamide gel electrophoresis showed *in vitro*-synthesized poly(A) comigrating with *in vivo*-synthesized poly(A). It is concluded that any RNA labeled *in vitro* with [^{3}H]-uridine triphosphate found to contain poly(A) must have received poly(A) synthesized during the *in vitro* incubation period.

2937 METHYLATED, BLOCKED 5' TERMINI IN HeLa CELL mRNA. (Eng.) Furuichi, Y. (Roche Inst. Mol. Biol., Nutley, N.J.); Morgan, M.; Shatkin, A. J.; Jelinek, W.; Salditt-Georgieff, M.; Darnell, J. E. *Proc. Natl. Acad. Sci. USA* 72(5):1904-1908; 1975.

The presence of terminal $m^7G(5')$ ppp(5')N^m-Np "caps" on HeLa cell messenger RNA (mRNA) was studied. Sus-

pension cultures of HeLa cells were grown in Eagle's medium and labeled with ^{32}P or [*methyl*^{3}H]methionine. Enzymatic digestion of mRNA was accomplished with RNase T_2, RNase A, *Penicillium* nuclease (P_1), bacterial alkaline phosphate (BAP), and/or nucleotide pyrophosphatase. Nucleotide and oligonucleotide analysis included column chromatography on DEAE-cellulose high voltage electrophoresis alone and coupled with DEAE paper electrophoresis, and descending paper chromatography. HeLa cells exposed to [*methyl*-^{3}H]methionine were found to contain radioactivity in poly(A)-terminated molecules the size of mRNA. Further analysis on the labeled oligonucleotides eluted from DEAE revealed two "caps". "Cap 1" consisted of m^7G and a second methylated nucleoside of 2'-*O*-methylguanosine and/or 2'-*O*-methyluridine; "cap 2" contained two adjacent 2'-*O*-methylated nucleosides, one of which was retained in the P_1-resistant portion of the cap. Enzymatic digestion of mRNA followed by a "two-dimensional fingerprint" demonstrated the presence of a variety of "capped" structures in HeLa cell mRNA (designated 0.5-1 cap 1 mRNA molecule) and the presence of N^6mA. Studies on the localization of the methylated nucleotides within HeLa cell mRNA showed about 33% of the [*methyl*-^{3}H]methionine in N^6-methyl-adenylic acid after RNase T_2 digestion, indicating that it is not adjacent to the capped 5' terminus. HeLa cell mRNA appeared to contain several forms of 5'-terminal, "capped" oligonucleotide structures. All were terminated with m^7G linked *via* three phosphates to either A^m, G^m, U^m, or C^m. The methylated cap structures were grouped into two general types: $m^7G\ pppN^m\text{-}N^p$ and $m^7Gp^ppN^m\text{-}N^m\text{-}NP$. The great variabilities observed suggest important effects of cell growth conditions of the composition of caps in mRNA.

2938 CONTROL OF rRNA SYNTHESIS: EFFECT OF PROTEIN SYNTHESIS INHIBITION. (Eng.) Franze-Fernández, M. T. (Departamento de Química Biológica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, Buenos Aires, Argentina); Fontanive-Sanguesa, A. V. *FEBS Lett.* 54(1):26-29; 1975.

The time required to synthesize the 45S ribosomal RNA (rRNA) precursor in control and protein synthesis-inhibited Ehrlich ascites tumor cells was determined. [^{3}H]uridine was added to cell cultures (1 x 10^6 cells /ml) and the incubation was continued for periods ranging from 7-18 min. Other cells were incubated for 90 min, after which 0.25 μg/ml pactamycin was added and the incubation was continued for 15 min; the cells were then labeled for 8-33 min. The amount of labeled RNA was determined by polyacrylamide gel electrophoresis. At 14 and 18 min pulses of [^{3}H]uridine, a small peak of radioactivity appeared at the 32S position in the gels from control cells. No 32S peak appeared, even after 30 min of labeling, in the gels from cells incubated with pactamycin. After an initial delay of about 5.5 min, radioactivity increased linearly in cells incubated without pactamycin. This delay reflected the time at which linear incorporation of the label into total RNA began, plus the time required to transcribe a complete 45S RNA chain. Incorporation of [^{3}H]uridine into total RNA was linear after a lag of two min. The transcription time of the rRNA precursor was twice the difference between the time lag found in the 45S species alone and that in total RNA, or about seven min. [^{3}H]uridine incorporation into 45S rRNA was not linear for labeling times under 18 min in cells incubated with pactamycin. When the pactamycin-treated cells were labeled for longer periods, incorporation became linear and extrapolated back to a time of about 12 min. Since the time at which linear incorporation of [^{3}H]uridine into total RNA began is identical in both control and pactamycin-treated cells, it is estimated that the time required to synthesize the complete 45S rRNA chain after a short period of protein synthesis inhibition is about 20 min, or three times as long as in controls. These results suggest that a short-lived protein(s) controls the rate of transcription of the genes coding rRNA.

2939 LIPID COMPOSITION OF THE MOUSE SPLEEN IN RAUSCHER LEUKAEMIA. (Eng.) Redai, I. (University Medical Sch., H-4012 Debrecen, P.O.B. 17, Hungary); Kiss, J.; Kasa, M. *Acta Microbiol. Acad. Sci. Hung.* 22(3):291-298; 1975.

Lipid content of spleens from Balb/c mice was determined 10, 14 and 18 days after infection with Rauscher virus. Spleen homogenates from mice with leukemia were centrifuged at 12,000 x *g*, and mice were infected ip with 0.2 ml supernatant. At the designated times after infection, the animals were exsanguinated, and protein and lipid content of the spleens was determined in control and infected mice. Polar and neutral lipids were separated from raw lipid by thin layer chromatography, and phospholipids were separated by two-dimensional thin layer chromatography on 500 μ Silicagel-G plates impregnanted with 0.01 M sodium carbonate. The same phospholipids were present in normal and Rauscher-infected spleens, but the distribution differed. Phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol were increased in infected animals (42.6, 19.4, and 8.1%, respectively) compared to controls (35.4, 13.9, and 5.2%, respectively), while the total amount of phospholipids decreased from 0.101 mg/mg protein at day 0 to 0.040 at day 18. Likewise, total lipids and neutral lipids decreased (0.190 to 0.090 mg/mg protein, and 0.090 to 0.050, respectively). Free fatty acids accumulated to 171% of controls by day 14, and triglyceride levels in infected spleens fell to 56% of controls by day 14. Result of ^{32}P (2 μCi/g, ip) uptake experiments confirmed that there was a decreased synthesis of phospholipids by tumor cells at 1-4 hr after injection. This study demonstrates that lipid types are unchanged by Rauscher virus infection, but that there is a quantitative difference in the components so that total lipid content decreases with progression of the tumor and free fatty acids accumulate.

2940 STUDIES OF THE REGULATION OF PURINE NUCLEOTIDE CATABOLISM. (Eng.) Lomax, C. A. (Cancer Res. Unit, Univ. Alberta, Edmonton, Canada); Bagnara, A. S.; Henderson, J. F. *Can. J. Biochem.* 53(2):231-241; 1975.

Different rates of purine nucleotide catabolism were produced by varying the concentration of 2-deoxyglucose in culture in order to investigate the regulation of enzyme activities in intact Ehrlich ascities tumor cells. Tumor cells were incubated with 5.5 mM glucose for 20 min; 100 μM [^{14}C]adenine was added, and incubation was continued for 30 min to synthesize [^{14}C]ATP. The same procedure was followed to prepare cells containing [^{14}C]GTP. Unutilized purine bases were removed and ATP or GTP catabolism was induced by resuspending the cells in medium containing 5.5 mM deoxyglucose or mixtures of glucose and deoxyglucose with a final total hexose concentration of 5.5 mM or with 50 or 100 μM 2,4-dinitrophenol in the absence of glucose. The concentrations of radioactive purine nucleotides, nucleosides, and bases were measured during the course of nucleotide catabolism. From these data, the apparent activities of enzymes of nucleotide catabolism were calculated. The linear relationship between the amount of adenylate deaminated and the amount formed suggested that the latter is the major factor in the determination of the rate of adenylate deaminase activity. The ATP concentrations did not markedly affect adenylate deaminase activity except as source of the substrate. A linear relationship was also seen between inosinate dephosphorylation and formation, suggesting that a major regulatory factor is the rate of inosinate formation. A few points, however, deviated from this linear relationship and these points corresponded to the experimental conditions that lead to the accumulation of radioactive inosinate to concentrations greater than 500 nM/g. A linear relationship was also seen between the rate of adenylate dephosphorylation and adenylate formation except under those conditions that led to the accumulation of radioactive adenylate to concentrations greater than 200 nM/g. Dehydrogenation of inosinate proceeded at a much slower rate than dephosphorylation, but a linear relationship was again seen between the amount of inosinate dehydrogenated and the amount formed, except under conditions that led to the accumulation of radioactive inosinate to concentrations greater than 150 nM/g. Dinitrophenol induced ATP catabolism by a different mechanism than deoxyglucose. The major products of dinitrophenol-induced ATP catabolism were mainly the nucleoside monophosphates, whereas these tended to be dephosphorylated when ATP catabolism was induced by deoxyglucose. Although the basis for this difference is not clear, it is concluded that substrate concentration is not highly important in the regulation of these processes.

2941 IMBALANCE OF PURINE METABOLISM IN HEPATOMAS OF DIFFERENT GROWTH RATES AS EXPRESSED IN BEHAVIOR OF GLUTAMINE-PHOSPHORIBOSYLPYROPHOSPHATE AMIDOTRANSFERASE (AMIDOPHOSPHORIBOSYLTRANSFERASE, EC 2.4.2.14). (Eng.) Prajda, N. (Indiana Univ. Sch. Medicine, Indianapolis, Indiana 46202); Katunuma, N.; Morris, H. P.; Weber*, G. *Cancer Res.* 35(11/Part 1):3061-3068; 1975.

The behavior of glutamine-phosphoribosylpyrophosphate amidotransferase was determined in normal, differentiating, and regenerating liver and in a spectrum of hepatomas of widely different growth rates. The liver and tumor enzymes were measured in 100,000 x *g* supernatants prepared from 20% tissue homogenates containing 0.25 M sucrose and 1 mM $MgCl_2$. Kinetic studies were carried out on the amidotransferase in the crude supernatant from liver and rapidly growing hepatoma 3924A so that under optimum standard assay conditions only the enzyme amount would be the limiting factor. The liver and hepatoma enzyme exhibited apparent Km values for: glutamine, 1.7 and 2.3 mM; $MgCl_2$, 0.7 and 1.1 mM, and phosphoribosylpyrophosphate. $S_{0.5}$ for 0.9 and 0.4 mM, respectively. The liver amidotransferase showed a sigmoid curve for phosphoribosylpyrophosphate, but under the same conditions the behavior of the hepatoma amidotransferase was similar to Michaelis-Menten kinetics. The liver and hepatoma enzymes exhibited a pH optimum at approximately 6.5-7.2. However, the plateau for liver was broad, but for the tumor it was sharp. Neither enzyme had activity under pH 4.8. At and above pH 9.0 the hepatoma exhibited no amidotransferase activity; however, the liver enzyme retained approximately 50% of its maximal activity. A standard assay was developed for liver and hepatoma in which good proportionality was achieved over a 120-min incubation period and with various amounts of enzyme added. In a spectrum of hepatomas, where the growth rate of the various tumor lines was 12.4-0.5 mo, the amidotransferase activity in the average cell was significantly increased in all neoplasms to approximately 175-256% of the values observed in the normal liver of control rats of the same strain, sex, age, and weight. In the regenerating liver the amidotransferase activity in the average cell was significantly increased at 24 hr (142%), 48 hr (181%), and 72 hr (124%) after partial hepatectomy above the values observed in the sham-operated control liver. The activity returned to normal 96 hr after operation. In postnatal differentiation the amidotransferase activity in the average liver cell at 1, 6, 18, and 25 days of age was 45, 46, 50, and 59%, respectively, of the activity observed in the liver of the normal adult rat. Since the tumor amidotransferase was increased in activity, it exhibited more favorable kinetics for phosphoribosylpyrophosphate and was less inhibited by AMP; these changes in the activity and molecular properties of this key purine-synthesizing enzyme should provide an increase in the capacity of the purine-synthetic pathway. These alterations in gene expression, which are manifested in the behavior of amidotransferase in the hepatoma, should confer selective advantages to the neoplastic cells.

2942 FOLATE METABOLISM IN THE RAT LIVER DURING REGENERATION AFTER PARTIAL HEPATECTOMY. (Eng.) Barbiroli, B. (Istituto de Chimica Biologica e di Biochimica Applicata dell'Universita di Bologna, Via Irnerio 48, 40126 Bologna, Italy); Bovina, C.; Tolomelli, B.; Marchetti, M. *Biochem. J.* 152(2):229-232; 1975.

Folate metabolism was studied during the early phases of liver regeneration after partial hepatec-

tomy in seven-wk-old male Wistar rats accustomed to eating during the first eight hours of a daily 12-hr dark period. The content of 5-methyltetrahydrofolate was drastically decreased during the first hours of regeneration. The total HCO-H_4-folate coenzymes showed a constant decrease during the first three days of regeneration, and a continuous interconversion between 5-HCO-H_4folate and 10-formyltetrahydrofolate. 10-Formyltetrahydrofolate synthetase, serine hydroxymethyltransferase, and 5,10-methylenetetrahydrofolate dehydrogenase activities were relatively low during the first hours after the operation, and increased only several hours later. The increase in enzyme activities showed a stepwise pattern, apparently due to an interaction between the regeneration process and the controlled feeding schedules.

2943 INCREASED PARTICULATE AND DECREASED SOLUBLE GUANYLATE CYCLASE ACTIVITY IN REGENERATING LIVER, FETAL LIVER, AND HEPATOMA. (Eng.) Kimura, H. (Dept. Intern. Medicine, Univ. Virginia, Charlottesville); Murad, F. *Proc. Natl. Acad. Sci. USA* 72(5):1965-1969; 1975.

The activities of soluble and particulate guanylate cyclase were determined in regenerating rat liver, fetal and neonatal rat liver, and hepatoma. Male Sprague-Dawley rats were partially hepatectomized; immediately afterwards, some of these rats were injected ip with 0.1 mg/100 g cycloheximide. Female ACI rats were inoculated sc with Morris hepatoma 3924A 47 days before sacrifice. Guanylate cyclase activity was determined by radioimmunoassay of cyclic GMP formed in culture. These tissues showed increased particulate and decreased soluble enzyme activities in comparison to normal adult rat liver. The particulate activity increased 12 hr after partial hepatectomy, reached maximal acyme activity decreased within eight hours and continued to decline. The activity of homogenates did not change. Guanylate cyclase activity was increased in plasma membrane and microsome fractions from regenerating liver. Cycloheximide prevented the increase in particulate guanylate cyclase activity and the increased incorporation of L-^{3}H-leucine (10 μCi, ip, 30 min prior to sacrifice) into protein after the partial hepatectomy. Decreased soluble and increased particulate enzyme activities were found in fetal liver. After birth, the soluble activity increased and the particulate activity decreased. Seven to 14 days after birth, the activities of soluble and particulate fractions were similar to those of adult rat liver. In hepatoma 3924A, the activity of particulate guanylate cyclase was 9-fold greater and that of the soluble enzyme was 50% that of normal liver. The results suggest that guanylate cyclase activity and its subcellular distribution may be related to liver growth through some unknown mechanism.

2944 ULTRASTRUCTURAL EVIDENCE OF ECTOGLYCOSYLTRANSFERASE SYSTEMS. (Eng.) Porter, C. W. (Grace Cancer Drug Center, Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14263); Bernacki, R. J. *Nature* 256(5519):648-650; 1975.

The plasma membrane localization of an N-acetylneuraminic acid ectoenzyme system (ectosialyltransferase) in murine leukemic L-1210 cells was demonstrated by electron microscope (EM) autoradiography. The cells were obtained from the ascites fluid of DBA/2 female mice, washed in phosphate-buffered saline (PBS), pH 7.4, and incubated in PBS containing 10 μM cytidine monophosphate ^{3}H-N-acetylneuraminic acid (CMP-^{3}H-NANA) for 15 or 60 min at 37 C. Pretreatment of cells with *Vibrio cholerase* neuraminidase increased the available endogenous cell-surface acceptor sites for ectosialyltransferase and the incorporation of label without affecting cell viability. After incubation, the cells were processed by a method ensuring that only the monosaccharide incorporated into glycoprotein was retained. EM autoradiographs of L-1210 cells incubated for 15 min with CMP-^{3}H-NANA consistently showed grains over the plasma membrane of the cell, whereas in cells labeled with ^{3}H-galactose the grains were concentrated mainly over the Golgi apparatus. ^{3}H-NANA incorporation ranged from 22,248 disintegrations/min/10^7 cells after a 15-min incubation to 121,071 after a 60-min incubation. The incorporation of ^{3}H-NANA directly onto the external plasma membrane glycoconjugate from its nucleotide monosaccaride differs from that of free monosaccharides, which are ordinarily incorporated by multiple activation steps in the Golgi apparatus (as exemplified with galactose). The methodology used in this study will enable a more direct assessment of the role of ectoglycosyltransferases in cell behavior.

2945 BIOSYNTHESIS OF CHONDROITIN 4-SULFATE-PROTEOGLYCAN BY A TRANSPLANTABLE RAT CHONDROSARCOMA. (Eng.) Stoolmiller, A. C. (Mental Retardation Res. Center, Univ. Chicago, Chicago, Ill. 60637); Schwartz, N. B.; Dorfman, A. *Arch. Biochem. Biophys.* 171(1):124-135; 1975.

The activities and subcellular distribution of five glycosyltransferases involved in the biosynthesis of chondroitin sulfate by a transplantable rat chondrosarcoma were compared with the activities and distribution of the corresponding enzymes of normal embryonic rat and chick cartilage. Two important differences were found: (a) uridine diphosphate-D-xylose (UDP-xylose):core protein β-D-xylosyltransferase ratio was 10-15 times higher in the chondrosarcoma, and (b) five glycosyltransferases were found to be more soluble in the chondrosarcoma. More than 90% of the xylosyltransferase activity could be extracted from the tumor without rupturing cells. This transferase exhibited optimal activity in solutions of 0.25 M KCl. The K_m for the exogenous protein acceptor obtained by Smith degradation of bovine chondroitin sulfate-proteoglycan was 300 μg/ml; the K_m for Ser-Gly-Gly, 30 mM. The activity of xylosyltransferase was maximal at pH 6.5 and was dependent upon the presence of Mg^{2+} and Mn^{2+}. The K_m for UDP-xylose was 5×10^{-5} M. The extraordinarily high level of xylosyltransferase activity found in the chondrosarcoma suggests a possible defect in the control of the synthesis of this enzyme. The authenticity of the xylosyl transfer reaction was verified by chemical charac-

ization of [^{14}C]xylose-labeled products. The id production of chondroitin sulfate-proteo-can by chondrocytes of the sarcoma could provide echanism by which the biosynthetic enzymes are ried into the extracellular fluid of the tumor.

6 α-GLUCOSIDASE ACTIVITY IN REFERENCE TO GLY-COGEN STORAGE, AND FORMATION OF GLYCOGENO-MES IN ASCITES HEPATOMA AH13 CELLS. COMPARISON OF 13 CELLS WITH ASCITES HEPATOMA AH109A AND NORMAL VER. (Eng.) Kojima, H. (Kumamoto Univ. Medical h., Kumamoto, Japan). *Kumamoto Med. J.* 28(1):1-7; 75.

Glucosidase activity was assayed in AH13 and AH109A cites hepatoma and in normal liver from male Donryu ts in order to determine the significance of the ffering glycogen contents of the two types of hepa-ma. After homogenization and fractionation, glyco-n was estimated by the anthrone reaction. α-Gluco-dase activity was estimated by the formation of glu-se from maltose at 37 C after one hour; the glucose s determined by the glucose oxidase method. Two pes of isoenzymes of α-glucosidase were found in 13, AH109A and normal rat liver. One was the acid glucosidase localized in the lysosomal fraction, d the other the neutral α-glucosidase found in the pernatant fraction. The activities of these two pes of α-glucosidase in AH13 cells were lower than ose in AH109A cells and normal rat liver. The de-ated α-glucosidase activity in AH13 cells is con-uded to be one of the regulatory factors for gly-gen accumulation and formation of glycogenosomes.

47 N-ACETYL-β-GLUCOSAMINIDASE ACTIVITY IN NORMAL AND MALIGNANT LEUKOCYTES. (Eng.) eed, C. E. (Univ. Rochester Cancer Center, 601 Elm-ood Ave., Rochester, N.Y. 14642); Bennett, J. M. *Histochem. Cytochem.* 23(10):752-757; 1975.

n applying a cytochemical method for demonstrating he lysosomal enzyme, N-acetyl-β-glucosaminidase, in eripheral blood and bone marrow, preference was ound for the use of fast garnet GBC over the use f hexazonium pararosaniline. When the hexazonium ararosaniline was used, diffuse staining in mono-ytes was noted. With fast garnet GBC, however, nzyme activity appeared as bluish-purple granules, nabling an actual count of the numbers of granules er cell. A lack of persistence of reactivity was drawback only if scoring was not done after stain-ng, or if a permanent file was required. In normal eripheral blood, monocytes consistently showed ac-ivity throughout the cytoplasm and over the nucleus, hile lymphocytes and neutrophils showed only mini-al reactivity. Basophils, eosinophils, RBC, and latelets were negative. Occasionally, increased ctivity was observed in polymorphonuclear leuko-ytes, but the average number of granules per cell as clearly higher in monocytes. When the N-acetyl-3-glucosaminidase reaction was carried out on peri-heral blood smears of seven patients exhibiting an increased absolute monocyte count greater than 800/ mm^3, an average of 34 granules/cell was observed. This was significantly higher than the average of 11 granules/cell observed for corresponding smears of 25 controls. Of 11 cases of predominantly mono-cytic leukemia, ten had elevated scores for the en-zyme; of 29 cases of acute myelo-monocytic leukemia, 21 had high scores; and of 15 cases classified as acute myeloblastic leukemia, all but four had low scores. The results point to the possible useful-ness of the enzyme as a monocyte marker.

2948 IDENTITY, RELEASE, AND BINDING OF MITOCHON-DRIAL-BOUND HEXOKINASES IN MAMMARY GLANDS AND ADENOCARCINOMAS OF LACTATING MICE. Bartley, J. C. (Children's Hosp. Medical Center of Northern Cali-fornia, Oakland, Calif. 94609); Barber, S.; Abraham, S. *Cancer Res.* 35(7):1649-1653; 1975.

The mitochondrial-bound hexokinases (ATP:D-hexose 6-phosphotransferase) of mammary adenocarcinoma and of normal gland were compared in lactating C3H/Blmrl mice. Some of the tumors used arose spontaneously in old mice, and some were from a transplanted line. Treatment of mitochondria isolated from both the nor-mal and neoplastic tissue with 0.5 M NaCl or 0.1 mM glucose 6-phosphate effected the release of about 50% of the bound hexokinase. In the presence of Mg^{+2} en-zyme from either source attached to mitochondria from either tissue and in all combinations to the same ex-tent. Identification of the isoenzyme complement in the mitochondrial extract by diethylaminoethylcellu-lose chromatography revealed only types I and II. In the tumor, the hexokinase activity in both the cytosol and the fraction solubilized from mitochondria was predominantly in the form of type I (∿60%). In con-trast, the activity released from mitochondria iso-lated from normal gland was predominately type II, while the cytosol contained almost equivalent amounts of types I and II. The difference in the complement of released hexokinase may provide a useful means of distinguishing between normal and neoplastic tissue.

2949 PROPORTIONAL ACTIVITIES OF GLYCEROL KIN-ASE AND GLYCEROL 3-PHOSPHATE DEHYDROGEN-ASE IN RAT HEPATOMAS. (Eng.) Harding, J. W., Jr. (Dept. Chem., Univ. Delaware, Newark); Pyeritz, E. A.; Morris, H. P.; White, H. B., III. *Biochem. J.* 148(3):545-550; 1975.

The activities of glycerol 3-phosphate dehydrogenase, glycerol kinase, lactate dehydrogenase, "malic" en-zyme (L-malate-NADP$^+$ oxidoreductase), and the β-oxo-acyl-(acyl-carrier protein) reductase component of the fatty acid synthetase complex were measured in nine hepatoma lines (eight in rats, one in mouse) and in the livers of host animals. With the single exception of Morris hepatoma 16, which had unusually high glycerol 3-phosphate dehydrogenase activity, the activities of glycerol 3-phosphate dehydrogenase and glycerol kinase were highly correlated in normal livers and hepatomas ($r=0.97$; $P < 0.01$). The lowest activities for both enzymes were found in the fast-growing Morris hepatoma 3924A and the highest activi-ties were found in the slower growing rat hepatomas 7787, 9618B, and the mouse tumor BW7756. In general, the activities of both enzymes increased with de-creasing growth rate as is typical of gluconeogenic enzymes. The activities of the two enzymes were not strongly correlated with the activities of any of the

other three enzymes. The primary function of hepatic glycerol 3-phosphate dehydrogenase appears to be in gluconeogenesis from glycerol.

2950 ISOENZYMES OF ALANINE ARYLAMIDASE (AAP, EC 3.4.11.2) AND GAMMA-GLUTAMYLTRANSPEPTIDASE (GGTP, EC 2.3.2.2) IN CHRONIC PANCREATITIS AND PANCREAS NEOPLASM. (Ger.) Bornschein, W. (II. Medizinische Klinik Rechts der Isar der Technischen Hochschule Munchen, Munchen, West Germany). *Clin. Chim. Acta* 61(3):325-333; 1975.

Gamma-glutamyltranspeptidase (GGTP), alanine arylamidase (AAP), and isoenzyme patterns were studied in sera from 22 patients with chronic pancreatitis and from 16 patients with neoplasms of the pancreas. Gel electrophoresis on agar revealed two fractions of AAP and GGTP isoenzymes: alpha-1 and alpha-2 (GGTP between alpha-1 and beta-globulin). The alpha-1 fraction of AAP and GGTP seens to be a specific liver isoenzyme. The slower fraction of both enzymes was also detected in chronic pancreatic diseases and cholestatic diseases as well as in neoplasms of the liver, pancreas, and biliary tract. However, the practical importance of the findings is diminished by the large variation coefficients of the results. A significantly low ratio of alpha-1 to alpha-2 fraction (or beta-globulin) of AAP and GGTP was found in the group with neoplasms of the pancreas, and especially in the head of the pancreas as compared with the group with intrahepatic cholestasis. A narrow fraction, designated as isoenzyme 3, occurred in a few cases of tumors in the pancreatobiliary region; it was not organ-specific.

2951 PURIFICATION OF RNA-INSTRUCTED DNA POLYMERASE FROM HUMAN LEUKEMIC SPLEENS. (Eng.) Witkin, S. S. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021); Ohno, T.; Spiegelman, S. *Proc. Natl. Acad. Sci. USA* 72(10): 4133-4136; 1975.

Isopycnic separation of virus particles and their conversion to cores by nonionic detergents provided a successful method for purifying a reverse transcriptase from the spleen of a patient with chronic lymphocytic leukemia. Spleen cell supernatants were layered on discontinuous sucrose gradients; the material present in the 25-50% sucrose interface was removed and treated with 30% solid $(NH_4)_2SO_4$. Viral cores were prepared by treating the $(NH_4)_2SO_4$ precipitates with 1% Nonidet P-40 and 0.1 M dithiothreitol and 30-65% sucrose gradient centrifugation. Particles possesssing a density of 1.16 g/ml and encapsulating a 70S RNA and a RNA-instructed DNA polymerase (reverse transcriptase) were isolated. These particles were converted to cores with a density of 1.26 g/ml and containing the enzyme-RNA complex, in complete analogy to the known RNA tumor viruses of avian and murine origin. The reverse transcriptase was purified from the cores by column chromatography to a stage showing a single major protein band of 70,000 daltons in gel electrophoresis. The enzyme was capable of transcribing heteropolymeric RNA into DNA complements as demonstrated by specific back hybridization to template RNA. The leukemic spleen would appear to represent an important source of this enzyme, as well as other potentially important leukemia-specific reagents.

2952 INTERACTION OF NORMAL AND TUMOR TRANSFER RNA METHYLTRANSFERASES WITH ETHIONINE-INDUCED METHYL-DEFICIENT RAT LIVER TRANSFER RNA. (Eng.) Kerr, S. J. (Univ. Colorado Medical Center, Denver, Colo. 80220). *Cancer Res.* 35(11/Part 1): 2969-2973; 1975.

The transfer RNA methyltransferases from normal rat liver and Novikoff hepatoma were compared with respect to their base specificity, capacity to methylate, and reaction kinetics, using mixed *Escherichia coli* B transfer RNA (tRNA) and ethionine-induced, partially methyl-deficient tRNA from the livers of female Holzman rats. The pattern of base methylation of the two substrates was found to be different with the use of enzymes from either source. In particular, N^1-methylguanine methylation was 5-fold greater in the methyl-deficient rat liver tRNA. The enzymes from the two sources also showed differences in specificity of base methylation in either substrate, particularly in the percentage of N^2-methylguanine synthesized (49.7% and 25.5% for the rat liver and 60.8% and 45.0% for the Novikoff hepatoma *E. coli* and methyl-deficient tRNAs, respectively). Maximal velocities for the various base-specific enzymes were lower with the methyl-deficient rat liver tRNA, with the exception of the 1-methylguanine-specific enzymes. These enzymes from either rat liver or Novikoff hepatoma exhibited approximately a 2.5 fold greater maximal velocity with methyl-deficient rat liver tRNA. Although further studies are necessary for any conclusions on the interaction of mammalian tRNA methyltransferases to be drawn, alterations in the enzymes in tumor tissues are apparent from this study.

2953 FUNCTION AND PROPERTIES OF AMINOACYL TRANSFERASES AND AMINOACYL-tRNA SYNTHETASES IN RAT LIVER AND HeLa CELLS. (Eng.) Smulson, M. (Sch. Med. Dent., Georgetown Univ., Wash. D.C.); Lin, C. S.; Chirikjian, J. G. *Arch. Biochem. Biophys.* 167(2):458-468; 1975.

Elongation factors (EF) 1 and 2, and aminoacyl-tRNA synthetases, are heterogeneously distributed in sucrose gradients containing postribosomal extracts of HeLa cells. The highest activity of the enzymes was found in a 5-7S region which corresponds to sedimentation coefficients expected for the free enzymes, but considerable enzyme activity was present at higher S values. The two elongation factors were found in a 10-17S region, whereas the synthetase activity was broadly distributed between 7 and 26S. The 26S peak contained mainly the aminoacyl-tRNA synthetases for valine, isoleucine, leucine, lysine, and histidine. In contrast, the synthetases for methionine, phenylalanine, and serine were dominating in the 5-10S region of the gradients. Two regions of a sucrose gradient containing postribosomal cell extract were subjected to gel filtration on a cali-

ated Sepharose 6 B column. One of the samples contained enzymes with a sedimentation coefficient of 0-12S, and the other sample, serving as a control, contained free, noncomplexed enzymes. EF-2 and synthetases eluted from 10-12S material mainly as high molecular wt aggregates (M_r up to approximately 3 million), whereas the eluate of 5S material contained both enzymes in their free, nonaggregated forms. EF-1 and EF-2 activity was monitored during the purification of leucyl-tRNA synthetase from rat liver. At a stage where purification was 350-fold and the enzyme was essentially devoid of all other synthetase activities, significant EF-1 and EF-2 activity still remained with the enzyme. This complex from rat liver has an apparent molecular wt of 5×10^5.

2954 ELEVATED PLASMA SIALYLTRANSFERASE IN THE CANCER PATIENT. (Eng.) Kessel, D. (Wayne State Univ. Sch. Med., Detroit, Mich.); Allen, J. *Cancer Res.* 35(3):670-672; 1975.

Sialyltransferase levels were investigated in plasma from 65 patients with conditions such as rheumatoid arthritis and liver cirrhosis, from lactating women, from patients with neoplastic diseases and from normal donors. Enzymatic activity was measured in a system containing ^{14}C-labeled cytidine 5'-phosphate-sialic acid (acceptor), desialated fetuin (donor), $MnCl_2$, *N*-2-hydroxyethylpiperazine-*N*-2'-ethanesulfonic acid buffer (pH 6.5) and Triton X-100. Enzyme levels in normal plasma, lactation, liver cirrhosis or sickle cell anemia averaged 281 (counts/min radioactivity incorporated/mg protein during 30-min incubation at 37C). Rheumatoid arthritis, however, showed a level of 422. In cancer patients, 11 showed values within the normal range, 20 were in the enzyme range of that of rheumatoid arthritis and the remaining 33 patients exhibited higher enzyme levels than in any of the neoplastic plasma preparations. The results suggest that serum sialyltransferase might be a measure of tumor metastases. The relationship between drug therapy and plasma sialyltransferase should be investigated.

2955 HEPATOCELLULAR CARCINOMA AND A VARIANT ALKALINE PHOSPHATASE. (Eng.) Higashino, K. (Osaka Univ. Hosp., Fukushima-Ku, Osaka 553, Japan); Ohtani, R.; Kudo, S.; Hashinotsume, M.; Hada, T.; Kang, K. Y.; Ohkochi, T.; Takahashi, Y.; Yamamura, Y. *Ann. Intern. Med.* 83(1):74-78; 1975.

The usefulness of a variant alkaline phosphatase in the diagnosis of hepatocellular carcinoma, and the clinical, laboratory, and pathologic findings in patients with this enzyme are described. Alkaline phosphatase was extracted from liver or cancer specimens with *n*-butanol and was subjected to polyacrylamide gel electrophoresis. The dried gel was then subjected to densitometry. Sera were also screened for alpha-fetoprotein by a micro double diffusion method and the testing of alpha-fetoprotein was done by a single radial immunodiffusion method. The appearance of this enzyme was specific to hepatocellular carcinoma. In 13 cases of primary hepatoma, its prevalence was about 30%, while that of alpha-fetoprotein was 77%. The occurrence of this enzyme in sera of four patients, whose case histories are presented, with hepatoma was, accordingly, independent of the serum alpha-fetoprotein concentration, and also independent of the appearance of the Regan or the Nagao isoenzymes and of the serum alkaline phosphatase activity. Patients with the enzyme had a massive type of hepatocellular carcinoma with grade III differentiation by Edmondson's classification. The detection of this enzyme in serum may be of help in confirming the diagnosis of hepatoma.

2956 THE RELEASE OF HIGH-MOLECULAR-WEIGHT ALKALINE PHOSPHATASE AND LEUCINE AMINOPEPTIDASE INTO THE MEDIA OF CULTURED HUMAN CELLS. (Eng.) Singer, R. M. (Tufts Cancer Res. Center, Boston, Mass. 02111); White, L. J.; Perry, J. E.; Doellgast, G. J. *Cancer Res.* 35(11/Part 1):3048-3050; 1975.

Using exclusion from Sepharose 4B as a criterion, a high-molecular-weight form of alkaline phosphatase and of leucine aminopeptidase were found which were released into the culture media by the FL amnion cell line. A low-molecular-weight form of leucine aminopeptidase was also found to contribute to the total levels of this enzyme in the media. The levels of these enzymes increased during the growth cycle of the culture, paralleling the increase in cell density; this suggests that the two events may be related. This phenomenon in culture suggests a possible explanation for the appearance of similar enzyme forms in patient serum and fluids originating from diseased tissue.

2957 NATURE OF THE INCREASE IN RENAL ORNITHINE DECARBOXYLASE ACTIVITY AFTER CYCLOHEXIMIDE ADMINISTRATION IN THE RAT. (Eng.) Levine, J. H. (Medical Univ. South Carolina, 80 Barre St., Charleston, S.C. 29407); Nicholson, W. E.; Orth, D. N. *Proc. Natl. Acad. Sci. USA* 72(6):2279-2283; 1975.

The increase in rat renal ornithine decarboxylase activity after cycloheximide administration was studied in Holtzman rats to determine whether it was mediated primarily by intracellular events within the kidney, or was secondary to the action of pituitary or adrenocortical hormones, whose release was stimulated by the antimetabolite. Within 30 min, 250 μg of cycloheximide essentially abolished renal protein synthesis. Renal ornithine decarboxylase activity was reduced approximately 70% one hour after ip administration of doses of cycloheximide that also inhibited renal protein synthesis by 68-95% within one hour. Protein synthesis began to recover by the second hour, accompanied by a rise in decarboxylase activity. Peak ornithine decarboxylase activity was directly proportional to cycloheximide doses up to 250 μg; larger doses were inhibitory. Plasma corticosterone rose rapidly after cycloheximide treatment peaking at two hours. Corticosterone response was also dose-dependent up to 250 μg, but larger doses were inhibitory. Hypophysectomy greatly reduced baseline renal decarboxylase activity within nine hours, and all but abolished the increase in enzyme

activity normally seen after cycloheximide administration to the intact rat. The hypophysectomized animal exhibited apparent increased sensitivity to cycloheximide. As protein synthesis was recovering in the hypophysectomized animals, renal decarboxylase activity responded adequately to the injection of a crude pituitary extract. These data suggest that renal ornithine decarboxylase turnover is rapid, that the early fall in its activity after cycloheximide treatment reflects inhibition of new enzyme synthesis, and that the subsequent rise in decarboxylase activity requires the action of pituitary factors released in response to the stress of cycloheximide administration.

2958 SPERMINE INHIBITS INDUCTION OF ORNITHINE DECARBOXYLASE BY CYCLIC AMP BUT NOT BY DEXAMETHASONE IN RAT HEPATOMA CELLS. (Eng.) Theoharides, T. C. (Yale Univ. Sch. Medicine, New Haven, Conn. 06510); Canellakis, Z. N. *Nature* 255(5511): 733-734; 1975.

The induction of ornithine decarboxylase (ODC) activity in rat hepatoma cells by cyclic AMP (cAMP) and dexamethasone was studied. Induction by cAMP reached a maximal 4-fold increase after three hours and declined to basal levels after seven hours; dexamethasone induction reached a 6-fold increase after 12 hours, and continued for 20 hours. A comparative study of the types of induction revealed that 10^{-5} M spermine abolished the cAMP induction and depressed the ODC activity below basal level; 6 x 10^{-5} M spermidine was equally effective. However, neither concentration affected the dexamethasone-induced ODC activity. Neither cycloheximide nor actinomycin D affected the basal enzyme level. Cycloheximide abolished induction by both agents; actinomycin D completely inhibited induction by dexamethasone, but only partially inhibited induction by cAMP. The low effective concentration of spermine, its speed of action, plus its selective inhibition of cAMP-induced activity suggests a unique role for spermine and a post-transcriptional site of action for cAMP.

2959 CYCLIC AMP-MEDIATED INDUCTION OF ORNITHINE DECARBOXYLASE OF GLIOMA AND NEUROBLASTOMA CELLS. (Eng.) Bachrach, U. (Natl. Heart and Lung Inst., Bethesda, Md. 20014). *Proc. Natl. Acad. Sci. USA* 72(8):3087-3091; 1975.

When confluent cultures of C6-BU-1 glioma or N115 neuroblastoma cells were treated with norepinephrine or isoproterenol, and prostaglandin E_1 or adenosine. L-ornithine decarboxylase activity was increased significantly in both cultures. Ornithine decarboxylase activity was elevated in confluent C6-BU-1 glioma cells treated with dibutyryl adenosine-3':5'-cyclic monophosphate and theophylline, or after the glioma cells were fed with a serum-depleted medium in the presence of catecholamines and inhibitors of cyclic nucleotide phosphodiesterase. The activity of the enzyme increases 500- to 1000-fold, 2-6 hr after stationary-phase N115 neuroblastoma cells were fed with a serum-free medium, supplemented with phosphodiesterase inhibitors, plus adenosine, or plus prostaglandin E_1. This stimulation was antagonized by carbamoyl choline and blocked by actinomycin D or cycloheximide. These results suggest that cAMP is involved in the induction of ornithine decarboxylase of C6-BU-1 glioma and N115 neuroblastoma cells.

2960 IMP DEHYDROGENASE, AN ENZYME LINKED WITH PROLIFERATION AND MALIGNANCY. (Eng.) Jackson, R. C. (Indiana Univ. Sch. Med., Indianapolis); Weber, G. *Nature* 256(5515):331-333, 1975.

Activities of inosine 5'-monophosphate (IMP) dehydrogenase were measured in homologous normal and malignant rat tissues. Liver homogenates (10% wt/vol) were prepared in 0.25 M sucrose, pH 7.4. Supernatants (100,000 x g) were fractionated with ammonium sulphate, and the fraction precipitating between 30% and 40% saturation contained all the IMP dehydrogenase activity. This precipitate was assayed with spectrophotometry. Enzyme activity was significantly higher in 11 transplantable hepatomas than in livers of normal rats. Moreover, the increase in enzyme activity correlated with hepatoma growth rate, the most rapidly growing tumors showing a 13-fold increase in activity compared with normal liver. This relationship between cell proliferation and IMP dehydrogenase activity was further emphasized by the high activity found in regenerating liver and in thymus and spleen. In regenerating liver, enzyme activity rose six hours after partial hepatectomy and reached a peak of about five times the normal activity by 24 hr. In thymus and spleen, IMP dehydrogenase activities were 10.5 and 8.6 times, respectively, of the liver specific activity. The correlation between enzyme activity and cell proliferation was not absolute, as demonstrated by lower activities in neonatal liver (only 25% higher than the adult value) and in intestinal mucosa. The pH profiles of the liver and hepatoma enzymes were identical. Both enzymes were inhibited by excess NAD+ and both were subject to product inhibition by xanthosine monophosphate and by NADH. Absolute IMP dehydrogenase activity was low, even in the most rapidly dividing tissues, which suggests that it may be one of the key rate-controlling enzymes in nucleic acid biosynthesis. The ubiquitous increase of IMP dehydrogenase in hepatomas indicates the linking of this enzyme alteration with the neoplastic transformation. Superimposed on this reprogramming of gene expression is the positive correlation of enzyme activity with tumor growth rates, indicating that enzyme inbalance is also linked with the degree of expression of malignancy.

2961 STUDIES ON 17β-HYDROXYSTEROID DEHYDROGENASE IN HUMAN ENDOMETRIUM AND ENDOMETRIAL CARCINOMA. I. SUBCELLULAR DISTRIBUTION AND VARIATIONS OF SPECIFIC ENZYME ACTIVITY. (Eng.) Pollow, K. (Institut fur Molekularbiologie und Biochemie, Abteilung fur gynakologische Endokrinologie (Klinikum Steglitz), Frauenklinik Charlottenburg, Freie Universitat Berlin, Germany); Lubbert, H.; Boquoi, E.; Kreutzer, G.; Jeske, R.; Pollow, B. *Acta Endocrinol. (Kbh.)* 79(1):134-145; 1975.

ecific activity of 17β-hydroxysteroid dehydrogenase 17β-HSD) was measured in subcellular fractions of ormal endometrium at different phases of the mentrual cycle, and of endometrial carcinoma at differnt degrees of differentiation. The purity of fracions was determined by marker enzymes, RNA/DNA ratio r electromicrographs. Both in normal and neoplastic issue 17β-HSD activity was located mainly in mitohondria and microsomes. The specific activity of 7β-HSD in rough and smooth membranes was similar to hat in crude, double-washed microsomes, indicating hat the microsomal 17β-HSD was bound tightly to the embranes of the endoplasmic reticulum. While in ormal endometrium specific enzyme activity in subellular fractions depended on the phase of the cycle, n endometrial carcinoma it depended on the degree of ifferentiation of the tumors. Specific activity in subcellular fractions of endometrial carcinoma decreased with decreasing differentiation of the tumor. The highest values of 17β-HSD activity were found in mitochondria and microsomes of early secretory endometrium (factor 10 as compared to proliferative endometrium) and in particulate fractions of well differentiated carcinoma (factor 10 to ≫ 10 as compared to undifferentiated carcinoma). The considerable changes in enzymatic activity may indicate that human endometrial 17β-HSD acts as a modulator of estradiol activity: the accelerated transformation of estradiol to estrone during the secretory phase could act synergetically with the effect of progesterone, leading to the blocking of the proliferative stimulus of the estrogens during the cycle.

2962 HORMONAL INDUCTION OF TYROSINE AMINOTRANSFERASE ACTIVITY IN HOST LIVER AND HEPATOMA #7777 OF NORMAL AND COFACTOR-DEPLETED ANIMALS. (Eng.) Tryfiates, G. P. (West Virginia Univ. Medical Center, Morgantown, W. Va. 26506); Saus, F. L.; Morris, H. P. *J. Natl. Cancer Inst.* 55(4):839-841; 1975.

Induction of tyrosine aminotransferase (TAT) by hydrocortisone was studied during cofactor (pyridoxal phosphate) depletion in hepatoma-bearing BUF strain female rats. Pairs of rats were matched for weight and age, and one from each pair was fed *ad libitum* a diet lacking pyridoxine; the other rat (referred to as "pair-fed") was given the same diet supplemented with the vitamin, with the amount restricted to that consumed by the matched animal on the deficient diet. All animals were inoculated im with Morris hepatoma #7777 cells after 21 days on the respective diets. TAT specific activity was determined weekly in host liver and hepatoma, in the presence and absence of cofactor, and before and after the administration of hydrocortisone. Free and bound pyridoxal phosphate was estimate enzymatically. The average weight of hepatomas from pair-fed animals was 1.5 to 2-fold greater than that of hepatomas from animals on deficient diets. TAT activity of hepatomas was two times greater than that of host liver, and lack of dietary pyridoxine was without effect. Hormonal induction of enzymatic activity was maximal after the first week of tumor growth and subsequently reached minimal values. In pair-fed animals, tumor TAT was approximately 60% saturated with cofactor. In vitamin-deficient animals, only 6% of the tumor enzyme was saturated with the cofactor. The percent saturation of host liver TAT varied, with minimal values found in the vitamin-deficient animals. Hepatic and tumor pyridoxal phosphate content of pair-fed animals was unusually high (10 μg/g); in vitamin-deficient animals, only the coenzyme content of hepatomas was high (7.0 μg/g). The results indicate that the presence of the tumor altered the (a) specific activity level of TAT and tissue content of cofactor, (b) pattern of hormonal induction of the enzyme, and (c) effects of the absence of dietary pyridoxine on TAT induction observed in animals without tumors.

2963 MELANOCYTE-STIMULATING HORMONE PROMOTES ACTIVATION OF PRE-EXISTING TYROSINASE MOLECULES IN CLOUDMAN S91 MELANOMA CELLS. (Eng.) Wong, G. (Yale Univ. Sch. of Medicine, New Haven, Conn. 06510); Pawelek, J. *Nature* 255(5510):644-646; 1975.

The control of melanocyte-stimulating hormone (MSH) by cyclic AMP was studied in Cloudman S91 melanoma cells. Metaphase cells were synchronized by exposure to colchicine and MSH, actinomycin D, or cycloheximide. Tyrosinase activity was found to increase in response to MSH during the G2 phase of the cell cycle; the increase was not suppressed by either actinomycin D or cycloheximide. In nonsynchronized cells, MSH did not alter the decay of tyrosinase activity. MSH also apparently promoted the inactivation of an inhibitor of tyrosinase functions. Partial purification of tyrosinase affinity chromatography and subsequent activity studies confirmed the presence of tyrosinase inhibitors in the cells. A further purification procedure indicated that the same number of enzyme molecules were present in cells regardless of pretreatment with MSH. It is concluded that MSH does not promote the synthesis of new molecules of the soluble form of tyrosinase. The data suggest that the mode of action of MSH is to partially relieve an inhibition of the enzyme, and that cAMP control is exerted at a post-translational level.

2964 THE ANDROGENIC REGULATION OF THE ACTIVITIES OF ENZYMES ENGAGED IN THE SYNTHESIS OF DEOXYRIBONUCLEIC ACID IN RAT VENTRAL PROSTATE GLAND. (Eng.) Rennie, P. S. (Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, U.K.); Symes, E. K.; Mainwaring, W. I. P. *Biochem. J.* 152(1):1-16; 1975.

The restoration of mitosis and growth of the prostate gland of castrated Sprague-Dawley rats (270-300 g) by androgens provides an experimental system for studying the hormonal regulation of enzymes engaged in DNA replication. The most marked change in the many DNA polymerase activities found in prostate after androgenic stimulation was a 9S form using denatured DNA as a template. This enzyme increased 14-fold during four days of testosterone administration. Androgenic stimulation of castrated rats led to a 100-fold increase in prostate DNA ligase activity which was not mimicked in spleen extracts. Thymidine kinase provided a sensitive in-

dicator of the hormonal regulation of DNA replication. By electrophoretic criteria, one novel form of the enzyme appeared precisely with the onset of mitosis. Only one form (pI7.0) of the DNase activities in the prostate gland can be said to be active in DNA replication. Androgenic stimulation of the prostate gland led to the appearance of a component capable of denaturing or unwinding prostate DNA. This component was distinct from RNA or DNA polymerase activities on the basis of several physicochemical characteristics. The conspicuous feature of all the changes in enzyme activities evoked by androgens in the prostate gland is their tissue- and steroid-specificity. Such changes could not be mimicked in liver or spleen and the regulatory role of androgens could not be stimulated by other classes of steroid hormones. On the basis of studies with the anti-androgen cyproterone acetate, it is concluded that the changes are initially mediated by the androgen-receptor system and the high-affinity binding of 5α-dihydrotestosterone in the prostate gland.

2965 STUDY OF GROWTH HORMONE SECRETION IN LUNG CARCINOMA. (Eng.) Claeys-de Clercq, P. (Service de Medecine et d-Investigation Clinique de l-Institut J. Bordet, Bruxelles, Belgium); Levin, S.; Borkowski, A. *J. Cancer* 11(8): 565-569; 1975.

The possibility of ectopic growth hormone (HGH) secretion in 26 patients with lung carcinoma was studied by measuring plasma HGH during an oral glucose tolerance test (GTT). Only four patients had raised basal HGH concentrations and these were only slightly above normal, and did not result from an autonomous secretion since they were modified by the GTT. Five patients had a paradoxical response to glucose. In the other 18 patients, basal HGH was normal and remained within normal limits after glucose administration. No evidence for a significant ectopic HGH secretion was found. A slight ectopic secretion without increased plasma HGH concentrations cannot be excluded, since during the GTT some plasma HGH was measurable in most of our 26 patients. There was no correlation between plasma HGH and any other clinical or biological parameter, including clubbing.

2966 PRE-PROPARATHYROID HORMONE IDENTIFIED BY CELL-FREE TRANSLATION OF MESSENGER RNA FROM HYPERPLASTIC HUMAN PARATHYROID TISSUE. (Eng.) Habener, J. F. (Harvard Medical Sch., Boston, Mass. 02114); Kemper, B.; Potts, J. T., Jr.; Rich, A. *J. Clin. Invest.* 56(5):1328-1333; 1975.

The earliest precursor of parathyroid hormone (PTH) and the initial product of the gene for PTH was identified by translating messenger RNA (mRNA) isolated from human parathyroid tissue (5 g) from a patient with primary chief-cell hyperplasia. RNA translation was performed in a heterologous cell-free system derived from wheat germ. Three fractions of RNA were observable on a sucrose gradient; one fraction (C) was significantly more active in directing amino acid incorporation into protein. Fraction C, an 8-15S RNA, stimulated [^{35}S]methionine incorporation 30-fold over control (without added RNA). Radioimmunoassay of aliquots of the incubation with fraction C showed a parallel increase in immunoreactivity of PTH. About 30% of the protein synthesized in a wheat germ extract containing fraction C migrated at a single peak (CFP) on SDS-acrylamide gels. CFP migrated slower than either ProPTH or PTH on both urea-acid and urea-sodium dodecyl sulfate polyacrylamide gels, indicating that it was more acidic and larger than PTH. Immune precipitation studies and tryptic peptide analyses indicated a structural similarity between CFP and ProPTH; CFP contained within its structure the sequence of ProPTH. CFP shared antigenic determinants and tryptic peptides with PTH and ProPTH. In addition, the protein contained tryptic peptides not found in ProPTH. Sequential Edman degradation of [^{35}S]methionine-labeled CFP indicated that the NH_2-terminal sequence of CFP differed from that of ProPTH. The results indicate that the 8-15S RNA fraction from human parathyroid tissue contains a mRNA that directs PTH protein synthesis in a cell-free system, and that CFP is an early biosynthetic precursor of human PTH.

2967 CANCER AND ALTITUDE. DOES INTRACELLULAR pH REGULATE CELL DIVISION? (Eng.) Burton, A. C. (Dept. Biophys., Univ. West. Ontario, London, Canada). *Eur. J. Cancer* 11(5):365-371; 1975.

Since physiological acclimatization to higher altitudes produces changes in alkali-reserve in man and animals remaining at altitude, a possible correlation with statistics on cancer was investigated. Available data on registrations of cancer (International Committee Against Cancer) and of cancer deaths (World Health Organization) were analyzed for possible correlation of age-specific rates with a population-weighted mean altitude for each region surveyed. There is no "altitude-effect" below 60 or 65 yr, but a statistically significant negative correlation ($r > 0{\cdot}5$.$P < 0{\cdot}05$ in 8, $< 0{\cdot}01$ in 7) was found for older ages in 15 of 16 sets of independent data. The drug acetazolamide which is used to simulate acclimatization to altitude produces acid-base changes, and is reported to have produced relief of intractable pain in terminal cancer patients. Some diseased states, such as achlorhydria and emphysema, in which there are chronic disturbances of acid-base relations, exhibit unexpected cancer rates. Some other possible explanations of the apparent "altitude effect", particularly that it is related to inefficiency of collection of data at high altitudes, seem implausible.

2968 STUDY OF CHRONIC MYELOID LEUKEMIA BY MARROW CULTURE *IN VITRO*. (Fre.) Sultan, C. (Hopital Henri-Mondor, F 94010 Creteil, France); Marquet, M.; Joffroy, Y. *Nouv. Rev. Fr. Hematol.* 15(2):161-164; 1975.

2969 AUTORADIOGRAPHIC STUDY OF CULTIVATION OF HUMAN SCIRRHOUS CARCINOMA OF THE STOMACH

DIFFUSION CHAMBERS. (Rus.) Krutova, T. V. st. Chem. Phys., USSR Acad. Sci., Moscow, .S.R.); Aksiutina, M. S.; Lipchina, L. P.; Kor-, D. B. *Bull. Exp. Biol. Med.* 59(6):83-85; 5.

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977 EFFECT OF CELL DIVISION, CELL FUSION AND CO-CULTIVATION ON THE RELEASE OF PLASMIOGEN ACTIVATOR BY MOUSE MELANOMA [abstract]. (Eng.) yner, D. S. (Mt. Sinai Sch. Med., New York, N.Y.); hristman, J. K.; Newcomb, E.; Silagi, S.; Silvertein, S. C. *Fed. Proc.* 34(3):532; 1975.

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2979 CHARACTERISTICS OF FIBRINOLYSIN SECRETED BY CULTURED RAT BREAST CARCINOMA CELLS [abstract]. (Eng.) Wu, M. C. (Univ. Miami Sch. Med., Fla.); Schultz, D. R.; Yunis, A. A. *Fed. Proc.* 34(3):529; 1975.

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2981 IDENTIFICATION OF A PROTEIN WHICH SELECTIVELY REDUCES THE APPARENT BINDING AFFINITY FOR CYCLIC AMP IN HEPATOMA CELL EXTRACTS [abstract]. (Eng.) Stellwagen, R. H. (Univ. South. California Sch. Med., Los Angeles); Mackenzie, C. W., III. *Fed. Proc.* 34(3):543; 1975.

2982 GLYCOPROTEINS ISOLATED FROM THE PLASMA MEMBRANE OF LYMPHOCYTES MAINTAINED IN LONG TERM CULTURE [abstract]. (Eng.) O'Brien, K. J. (Med. Sch., Univ. Minnesota, Minneapolis); Edstrom, R. D. *Fed. Proc.* 34(3):615; 1975.

2983 CHEMICAL STRUCTURE OF PARAPROTEINS OF MYELOMAS. (Eng.) Roholt, O. A. (Dept. Immunology and Immunochemistry Res., Roswell Park Mem. Inst., Buffalo, N.Y.); Seon, B.-K.; Grossberg, A. L.; Pressman, D. *Transplant. Proc.* 7(2):215-218; 1975.

2984 AUTORADIOGRAPHIC DEMONSTRATION OF DNA REPLICATION IN ULTRATHIN SECTIONS OF PLASTIC-EMBEDDED TISSUES USING AN EXOGENEOUS DNA POLYMERASE. (Eng.) Geuskens, M. (Institut de Recherches Scientifiques sur le Cancer, Villejuif, France); de Recondo, A. M.; Chevaillier, P. *Chromosoma* 52(2):175-188; 1975.

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2986 DNA SYNTHESIS BY AMV REVERSE TRANSCRIPTASE: TEMPLATE-SPECIFIC CATION EFFECTS [abstract]. (Eng.) Marcus, S. L. (Mem. Sloan-Kettering Cancer Cent., New York, N.Y.); Modak, M. J. *Fed. Proc.* 34(3):609; 1975.

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2988 CHARACTERIZATION OF NOVIKOFF HEPATOMA MESSENGER RNA METHYLATION [abstract]. (Eng.) Desrosiers, R. (Dep. Biochem., Michigan State Univ., East Lansing); Friderici, K.; Rottman, F. *Fed. Proc.* 34(3):628; 1975.

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National Cancer Institute

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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

Carcinogenesis Abstracts is normally published monthly. Volume XIII covers the scientific literature published from Jan 1975 through Dec 1975. To increase the usefulness of *Carcinogenesis Abstracts*, Volume XIII, a Wiswesser Line Notation index and a Chemical Abstracts Service Registry Number index have been provided. These indexes reference compounds described in abstracted articles. A cumulative subject, author, CAS Registry Number, and Wiswesser Line Notation index for Volume XIII will be published shortly after the final regular issue.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations found in *Chemical Abstracts Service Source Index*, 1907-1974 Cumulative, are used. New journals are verified in *New Serial Titles* and abbreviated according to *International Standard ISO 833*. An asterisk indicates the author to address (other than the primary) in requesting reprints.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	Ind.	Indonesian
Ara.	Arabic	Ita.	Italian
Bul.	Bulgarian	Jpn.	Japanese
Chi.	Chinese	Kor.	Korean
Cro.	Croation	Lav.	Latvian
Cze.	Czech	Lit.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
Eng.	English	Por.	Portuguese
Est.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fle.	Flemish	Ser.	Serbo-Croatian
Fre.	French	Slo.	Slovak
Geo.	Georgian	Spa.	Spanish
Ger.	German	Swe.	Swedish
Gre.	Greek	Tha.	Thai
Heb.	Hebrew	Tur.	Turkish
Hun.	Hungarian	Ukr.	Ukrainian
Ice.	Icelandic	Vie.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

A	angstrom(s)
ACTH	adrenocorticotropic hormone
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
BCG	Bacillus Calmette Guerin
bid	twice daily
C	degrees centigrade
cal	calorie(s)
kcal	kilocalorie(s)
cc	cubic centimeter(s)
Ci	curie(s)
mCi	millicurie(s)
μCi	microcurie(s)
cm	centimeter(s)
CNS	central nervous system
cpm	counts per minute
dl	deciliter(s)
ml	milliliter(s)
μl	microliter(s)
DNA	deoxyribonucleic acid
ED_{50}	median effective dose
EDTA	ethylenediamine tetraacetic acid
ESR	erythrocyte sedimentation rate
g	gram(s)
kg	kilogram(s)
mg	milligram(s)
μg	microgram(s)
Hb	hemoglobin
hr	hour(s)
ia	intra-arterial
ic	intracerebral
icav	intracavitary
id	intradermal
ILS	increased life span
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratumorous
IU	International Unit
iv	intravenous
K_m	Michaelis constant
LD	lethal dose
LD_{50}	median lethal dose
m	meter(s)
mm	millimeter(s)
M	molar
mM	millimolar
μM	micromolar
mOsm	milliosmolar
mEq	milliequivalents
min	minute(s)
mo	month(s)
MTD	maximum tolerated dose
N	normal concentration
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotidephosphate
NADPH	reduced nicotinamide adenine dinucleotide-phosphate
ng	nanogram(s) (10^{-9})
od	once daily
Pa	ambient pressure
PAS	periodic acid-Schiff
pg	picogram(s) (10^{-12})
pgEq	picogram equivalent
po	orally
ppb	parts per billion
ppm	parts per million
qid	four times daily
qod	every other day
QO_2	oxygen quotient
R	roentgen(s)
RBC	red blood cells (erythrocytes)
RNA	ribonucleic acid
sc	subcutaneous
sec	second(s)
SGOT	serum glutamic-oxalacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SRBS	sheep red blood cells
TCD	tissue culture dose
TCD_{50}	median tissue culture dose
tid	three times daily
U	unit(s)
mU	milliunit(s)
UV	ultraviolet
vol	volume
WBC	white blood cells (leukocytes)
wk	week(s)
wt	weight
x	times
yr	year(s)

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3001 USE OF EPITHELIAL CELL CULTURES FOR STUDIES ON THE MECHANISM OF TRANSFORMATION BY CHEMICAL CARCINOGENS. (Eng.) Weinstein, I. B. (Francis Delafield Hosp., New York, N.Y.); Yamaguchi, N.; Gebert, R. *In Vitro* 11(3):130-141; 1975.

Evidence is reviewed for and against four major theories of chemical carcinogenesis: somatic mutation; cell selection, including suppression of immune surveillance; virus activation; and enhancement differentiation. The development of several normal and transformed epithelial cell lines that should be useful for studies of the mechanisms of chemical carcinogenesis is described. Whereas none of five epithelial cell cultures established from normal liver synthesized RNA virus-like particles, five hematoma lines and a spontaneously transformed line gave definite evidence for production of RNA virus-like particles. A cell culture transformed with *N*-acetoxy-acetylaminofluorine did not release virus particles, but could be induced to do so after treatment with bromodeoxyuridine. The causitive, symptomatic, and cofactor hypotheses of rat hepatoma-associated virus are reviewed. The first theory postulates that a carcinogen activated the latent virus that provides the information for transforming the cell. Both the symptomatic and cofactor hypotheses are based on the assumption that carcinogens produce aberrations in the control of differentiation and activation of latent viral genomes. According to the former hypothesis, however, the virus is inert; the later hypothesis is based on the assumption that it contributes oncogenic information to the transformed cell. Additional studies of synergistic effects between either RNA or DNA viruses and chemical carcinogens are needed. Preliminary data are presented on the first mutants of chemically transformed epithelial cells that are temperature-sensitive in the maintenance of the transformed phenotype. The data show that the mutants have a temperature-sensitive lesion in a gene(s) controlling cell growth in agar, growth under agar, saturation density in monolayer cultures, cloning efficiency in monolayer cultures, and cell shape and surface morphology. Although the mutants show minimal features of transformation, they should be useful for detecting the critical biochemical changes that distinguish a chemically induced tumor from its normal counterpart. (84 references)

3002 EPIDERMAL CELL KINETICS AND CARCINOGENESIS. (Eng.) Iversen, O. H. (Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway). *Proc. Int. Cancer Congr. 11th.* Vol. 1 *(Cell Biology and Tumor Immunology).* Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 24-28.

The cellular organization of the epidermis is described, and the application of new methods to the study of cell kinetics and epidermal carcinogenesis is discussed. A description of the epidermis proper notes the normal structure of the interfollicular epidermis, the transit and maturation of basal cells to surface cells, and the mean generation time, transit time, and turnover time. The mechanism regulating the rate of cell proliferation in the basal layer, so as to balance exactly the surface cell loss, probably consists of a system of tissue-specific chemical regulatory substances. The S-factor (G_1-chalone) and the M-factor (G_2-chalone) are known to inhibit the progress of cells through the cell cycle. It is noted that most of the experimental evidence on epidermal cell kinetics and early carcinogenesis is based on situations employing one or few large applications of chemical carcinogens and irradiation. One single application of a strong hydrocarbon carcinogen primarily leads to a toxic "shock" phase which is followed by a proliferative phase of increased DNA synthesis and mitotic rate, then consequent transient hyperplasia. The initial blocking of DNA synthesis seems to follow all types of carcinogenic influences; alterations induced by promoting substances in two-stage carcinogenesis models are very similar to those induced by high doses of complete carcinogens. Repeated doses of carcinogens also have kinetic consequences, and regularly lead to a situation where both cell proliferation is moderately increased and cell maturation is disturbed. Many studies have indicated that cells may be more sensitive to carcinogens when they are in DNA synthesis, or that tissues with a high rate of cell turnover, e.g. rapidly dividing epidermal basal cells, are most sensitive to carcinogens. It is concluded that carcinogens provoke obvious changes in almost all parameters of the epidermal cell kinetics; however, it is unknown whether such changes are specific, or toxic and nonspecific. (23 references)

3003 BREAST CANCER AND ORAL CONTRACEPTION. (Eng.) Taber, B. Z. (Palo Alto, Calif. 94304). *J. Reprod. Med.* 15(3):97-99; 1975.

A review of human retrospective and prospective studies, and studies on dogs and monkeys, indicates no association between oral contraceptive intake and benign or malignant breast disease. (13 references)

3004 IMMUNOSUPPRESSIVE ANTICANCER DRUGS IN MAN: THEIR ONCOGENIC POTENTIAL. (Eng.) Harris, C. C. (Building 37, Room 3C03, Natl. Inst. Health, Bethesda, Md. 20014). *Radiology* 114(1):163-166; 1975.

Case reports of new cancers in patients treated with anticancer drugs have recently appeared. Animal studies indicate that alkylating drugs (nitrogen mustard), those that bind DNA (actinomycin D), and those that form electrophilic reactants, may be oncogens. Antimetabolites (methotrexate) may be co-oncogens. Radiation therapy closely followed by intensive chemotherapy may increase the risk of a second neoplasm in Hodgkin's disease. The use of these drugs to treat nonfatal diseases indicates the need for studies to evaluate the hazard in humans. (72 references)

3005 OCCUPATIONAL DISEASES OF THE LUNGS. PART II. INHALATION DISEASES DUE TO INORGANIC DUST. (Eng.) Wolf, A. F. (Scott and White Clinic, Temple, Tex. 76501). *Ann. Allergy* 35(2):87-92; 1975.

Occupational diseases of the lungs caused by inhalation of inorganic dusts are described. In general, most dusts are capable of irritating or fibrotic effects, depending on the particle size, concentration in the inhaled air, duration of exposure, and individual susceptibility. Silicosis, due to exposure to silicon dioxide (quartz dust), occurs in gold miners, granite and tombstone workers, sand blasters, foundry workers, and those exposed to potter's clay and diatomaceous earth. The importance of particle size, characteristic nodular and fibrotic lesions, roentgenographic patterns, and clinical evaluation is discussed in detail. Coal miners' pneumoconiosis, also referred to as anthracosis or anthracosilicosis, is due to the inhalation of a mixture of carbon, silica, and other dusts. The morphological changes due primarily to carbon deposition, the deposition around bronchioles and arterioles, and the disabling focal emphysema are described. The classification and symptomology of simple and progressive coal dust pneumoconiosis are discussed. Pneumoconioses due to graphite dust or iron dust exposure are also described. Asbestosis is also an important peumoconiosis, occurring chiefly in asbestos miners, but also in persons directly and indirectly exposed to the fiber. The significance of fiber length, the roentgenographic changes of fibrosis and focal emphysema, and the frequent lack of clinical symptoms are discussed. Complications due to bronchogenic carcinoma, bronchoalveolar carcinoma, and mesothelioma have been often reported in cases of asbestosis. Talcosis, resulting from exposure to magnesium silicate (tremolite talc) dust, affects miners, millers, and rubber workers; fibrosis and disabling symptoms are described. Nonpathological pneumoconiosis can also be due to radiopaque dusts of iron, tin, barium, antimony, and emery. Although a marked decrease of berylliosis has been observed, both chronic and acute forms are being found. Despite prior predictions, no pulmonary diseases have yet been ascribed to fiberglass exposure. Exposure to inorganic dusts may result in some roentgenographic similarities, but a wide range of symptoms of susceptibilities does occur. (No references)

3006 GENETIC DIFFERENCES IN SUSCEPTIBILITY TO CANCER AND TOXICITY CAUSED BY ENVIRONMENTAL CHEMICALS. (Eng.) Nebert, D. W. (Natl. Inst. Child Health and Human Development, Bethesda, Md.); Felton, J. S.; Robinson, J. R. *Proc. Eur. Soc. Study Drug Toxic.* 16:82-95; 1975.

Experimental data are presented showing that genetic differences in aromatic hydrocarbon responsiveness exist among various mouse strains, including inbred C57BL/6 (B6) and DBA/2 (D2) mice in progeny from various back- and inter-crosses. A responsive animal has higher inducible hydroxylase activities than a nonresponsive animal, not only in liver but in numerous nonhepatic tissues. About 11 inducible monooxygenase activities are known to co-segregate with increased hepatic cytochrome P_1-450 in aromatic hydrocarbon-treated responsive mice. Recent data indicate that hydroxylase induction by aromatic hydrocarbons is regulated by at least two genetic loci, instead of a single gene difference. By comparing responsive and nonresponsive siblings in 14 inbred mouse strains, it was possible to evaluate the susceptibility of each animal to various carcinogenic or toxic environmental agents. Tumorigenesis caused by the sc administration of 150 μg 3-methylcholanthrene, but not similar treatment with benzo(*a*)pyrene or with 7,12-dimethylbenz(*a*)anthracene, is highly correlated wih aromatic hydrocarbon responsiveness. Benzo(*a*)pyrene or 7,12-dimethylbenz(*a*)anthracene is more cytotoxic in cell cultures derived from responsive mice. Benzo(*a*)pyrene, 7,12-dimethylbenz(*a*)anthracene, or β-naphthoflavone given in large ip doses cause responsive mice to die earlier than nonresponsive mice; these data are in agreement with those found in cell cultures and suggest that the activation of these chemicals to toxic metabolites is associated with increased aromatic hydrocarbon hydroxylase activities. However, nonresponsive mice receiving po benzo(*a*)pyrene, 7,12-dimethylbenz(*a*)anthracene, 3-methylcholanthrene, or β-naphthoflavone die sooner than responsive mice. On the other hand, responsive mice receiving polychlorinated biphenyls po die sooner than nonresponsive mice. When given lethal ip doses of the insecticide lindane (300 mg/kg), 3-methylcholanthrene-treated nonresponsive mice died much earlier than 3-methylcholanthrene-treated responsive mice. These studies demonstrate the importance of genetic predisposition in determining the extent to which a foreign compound may be carcinogeneic or toxic to a particular individual. (52 references)

3007 RETROSPECTIVE SURVEY OF THE ALLEGED DISEASES ASSOCIATED WITH VINYL-CHLORIDE IN THE FEDERAL REPUBLIC OF GERMANY. (Eng.) Thiess, A. M. (6700 Ludwigshafen am Rhein, W. Germany); Frentzel-Beyme, R. *J. Occup. Med.* 17(7):430-432; 1975.

Various aspects and problems of conducting epidemiological studies of disease associated with vinyl chloride/polyvinyl chloride (VC/PVC) exposure in the Federal Republic of Germany are reviewed. According to a survey made in 1974, a total of 180 cases of vinyl chloride-related diseases has been recorded. Of that number, 132 cases were workers employed in VC/PVC production plants and 48 were employed in PVC processing factories. Only 57 of 180 original cases were recognized as being occupational illnesses according to expert opinion from the Occupational Medical Officer. Five cases of hemangioendotheliosarcoma have been established in Germany among workers exposed to vinyl chloride. Four of these cases, all men exposed to VC/PVC for 11-17 yr, have died. The only living subject (49 yr old) had been employed as an autoclave cleaner for 11.75 yr. Three research projects are currently being carried out on the health effects of vinyl chloride: (1) an investigation into metabolism and pharmacokinetics of vinyl chloride; (2) a study of the documentation, methods of assessment and analysis of vinyl chloride; and (3) an epidemiological investigation of health consequences due to vinyl chloride. Preliminary results from the epidemiological investigation indicate that there have been 201 deaths of vinyl chloride-exposed workers, 49 of which have been caused by cancer (25%). In an epidemiological investigation being conducted by BASF, only 46% of those workers who have ever been exposed to

vinyl chloride are traceable. In these studies, it is difficult, if not almost impossible, to determine whether persons were exposed only to vinyl chloride or if they also came into contact with a number of other chemical substances. Another serious difficulty in such epidemiological studies is determining the cause of death. Experience has shown that the causes of death stated on the death certificate do not always agree with the real cause. It is expected that a standard maximum working place concentration for vinyl chloride of 10 ppm will be established for the Federal Republic of Germany. (5 references)

3008 IS THERE A BASIC PROBLEM WITH CHLORINATION? (Eng.) Larson, C. D. (Operations Section Water Supply Branch EPA Region I). *J. New Engl. Water Works Assoc.* 89(3):225-232; 1975.

A review of the history of water chlorination is presented. Chlorination was first used on a regular basis in 1908. Since that time, no conclusive evidence has been presented that chlorine in drinking water is harmful. One study showed that there is a high potential capacity of the human oral mucosa to rapidly remove active chlorine from drinking water containing 1-10 mg/l of free chlorine. Feeding studies in rats indicated that residual chlorine concentrations up to and including 2.5 mg/l in drinking water over a six-month period were practically harmless. Although there is preliminary data indicating that raw water containing naturally occurring organic compounds such as humic acid or certain industrial wastes may produce suspected carcinogenic compounds when chlorinated, no conclusive epidemiological evidence has been obtained on the carcinogenicity of chlorinated water. It has been suggested that present chlorination practices are inadequate to maintain hygienically safe water supplies, and that the level should be increased to 1-2 ppm free chlorine after 10-30 min of contact time. (17 references)

3009 SUGGESTED REDUCTION OF PERMISSIBLE EXPOSURE TO PLUTONIUM AND OTHER TRANSURANIUM ELEMENTS. (Eng.) Morgan, K. Z. (Sch. Nucl. Eng., Georgia Inst. Techol., Atlanta). *Am. Ind. Hyg. Assoc. J.* 36(8):567-575; 1975.

The historical development of the maximum value set for permissible body burden of ^{239}Pu is outlined; present considerations for the revision of this standard are given. Some evidence is presented that the linear hypothesis may not be sufficiently conservative at low radiation dose rates; this is also especially true for the actinide elements. ^{239}Pu dispersed into the environment in very low concentrations delivers a protracted rather than an acute exposure to man; the risks may thus be greater than those suggested by studies in which animals were exposed to high levels of ^{239}Pu. The present values of organ burden and body burden of transuranium radionuclides are calculated on the basis of uniform distribution in the critical body organ. The assumption of a uniform distribution of a radionuclide underestimates the risk of bone cancer from ^{239}Pu. The radionuclide is deposited on bone surfaces of the trabecular matrices adjacent to the thin layer of endosteal tissue, which is the most critical tissue in this case. The use of a uniform distribution value also raises the question of the "hot particle" problem and the adequacy of a value of body burden or organ burden for ^{239}Pu based on the lung as the critical organ. The most reliable values of body burden based on the bone as the critical tissue can be obtained by comparing the incidence of bone carcinoma and sarcoma in dogs that have been injected with known amounts of ^{226}Ra and ^{239}Pu. Such studies suggest that the present maximum permissible body burden of ^{239}Pu should be reduced by at least a factor of 200. (23 references)

3010 CELL INJURY WITH VIRUSES. (Eng.) Tamm, I. (Rockefeller Univ., New York, N.Y. 10021). *Am. J. Pathol.* 81(1):163-178; 1975.

A review of literature concerning biochemical alterations that occur in cytocidal virus-cell interactions is presented. The inhibitions of cellular protein and RNA synthesis in picornavirus-infected cells are early events requiring only limited synthesis of virus-specific proteins. The inhibition of cellular protein synthesis appears to be due to blocking of the association of ribosomes with host messenger RNA. Inhibition of cellular RNA synthesis involves inactivation of the template-enzyme complex and affects ribosomal RNA synthesis before messenger RNA synthesis. Inhibition of cellular DNA synthesis also occurs early and may be secondary to inhibition of cellular protein synthesis. Early chromatid breaks may be related to inhibitions of cellular protein and nucleic acid synthesis. Stimulation of phospholipid synthesis in picornavirus-infected cells also requires only limited synthesis of virus-specific proteins. In contrast, release of lysosomal enzymes, proliferation of smooth cytoplasmic membranes, cellular vacuolization, retraction, and rounding, and diffuse chromosomal changes related to karyorrhexis and pyknosis are all dependent on considerable synthesis of virus-specific proteins during the middle part of the picornavirus growth cycle. The early virus-induced alterations in cellular biosynthetic processes are not the direct or sole cause of the subsequent marked pathologic changes in the membranes and chromosomes of the cell. (62 references)

3011 PART XV: TUMORS: STUDIES ON EPSTEIN-BARR VIRUS-ASSOCIATED ANTIGENS. (Eng.) Ernberg, I. (Karolinska Inst., S-10401 Stockholm 60, Sweden). *Ann. N.Y. Acad. Sci.* 254:516-522; 1975.

The Epstein-Barr virus (EBV) is discussed in association with three diseases in man, i.e., Burkitt's lymphoma, nasopharyngeal carcinoma, and infectious mononucleosis. The association of these diseases to EBV is based on the altered serological patterns, raised antibody titers against EBV-associated antigens, the presence of virus-associated antigens, and the discovery of viral genetic material. Studies of patient antibody reactivity to virus-associated antigens involve membrane antigens, early antigens, viral cap-

sid antigen, and Epstein-Barr viral nuclear antigen (EBNA). *In vitro* studies on lymphoblastoid cell lines, surface characteristics of B cells have been assigned to EBV-infected cells, and comparatively few EBNA sites per cell have been found. The cell lines containing EBV genetic material are classified into two groups, i.e., nonproducer and producer cell lines, depending upon their ability to synthesize viral DNA and late viral products. Such studies have demonstrated an additional membrane antigen, the late membrane antigen. The EBV genome in certain nonproducer cell lines can be induced to synthesize viral antigens *via* addition of iododeoxyuridine or bromodeoxyuridine. Antigen synthesis is also induced by superinfection of cell lines with purified EBV. The varying degrees of spontaneous expression of viral antigens suggests mechanisms of cellular control. The studies thus far have indicated that early membrane antigens, early antigens, viral capsid antigen, and late membrane antigens are associated with the virus-producing cycle. Other experiments have suggested that EBNA is still present in the cell when early antigen is synthesized. (70 references)

3012 EPSTEIN-BARR VIRUS (EBV). (Eng.) Klein, G. (Dept. Tumor Biology, Karolinska Institutet, S 104 01 Stockholm 60, Sweden). *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 282-287.

Research on the Epstein-Barr virus (EBV) is reviewed and the role of EBV in human malignancy is discussed. Six major findings are especially noted: (1) normal human lymphocytes do not grow as established lines *in vitro,* unless and until EBV is added; established lymphoblastoid lines then carry multiple viral genome equivalents/cell. (2) primary infection of young children with EBV leads to seroconversion but no clinically recognizable disease; however, primary infection of teenagers or young adults leads to acute infectious mononucleosis in 50% of the cases. (3) antibody titers against EBV-determined antigens are increased in various disease states; only two human neoplastic diseases, i.e., nasopharyngeal carcinoma and African Burkitt lymphoma cases tested, by nucleic acid hybridization and/or EBNA tests, contain the viral genome. (5) EBV can induce malignant lymphoproliferative disease in marmosets and owl monkeys; the resulting tumors carry the EBV genome. (6) poorly differentiated or anaplastic nasopharyngeal carcinoma cells also contain the EBV genome. There is thus no doubt that the EBV can transform normal lymphocytes into potentially malignant cells, can induce tumors in some nonhuman primates, and is capable of causing a self-limited lymphoproliferative disease. Several hypotheses of the role of EBV in human malignancy are then presented. The "passenger hypothesis," i.e., the notion that the ubiquitous EBV is a frequent contaminant of lymphoid tissue, is deemed untenable because the viral genome or its antigenic "footstep" (EBNA) is *not* found in the neoplastic cells of any human lymphoproliferative disease except African Burkitt's lymphoma. It is then postulated that primary infection and neoplastic transformation coincide closely in time, or, alternatively, that the neoplastic transformation responsible for African Burkitt lymphoma preferentially affects an EBV-genome carrying cell. Two main alternatives are presented; the "immunological hypothesis" suggests that the EBV-converted lymphoid cell requires additional change prior to attaining full malignant potential. It is also suggested that the EBV-genome negative non-African Burkitt lymphomas and the few (3%) genome negative African cases probably have a different, entirely EBV-unrelated origin. Speculations on the role of EBV in nasopharyngeal carcinoma also note the association of the viral genome and suggest a major genetic influence. Considering also the possible existence of different EBV variants of different oncogenic properties, the exact role of EBV in the neoplastic process is not yet resolved. (44 references)

3013 HUMAN HERPESVIRUSES. I: A MODEL FOR MOLECULAR ORGANIZATION OF HERPESVIRUS VIRIONS AND THEIR DNA. (Eng.) Roizman, B. (Dept. Microbiology, Univ. Chicago, Chicago, Ill.); Hayward, G.; Jacob, R.; Wadsworth, S.; Honess, R. W. *Proc. Int. Cancer. Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 188-198.

Current knowledge concerning the molecular organization of Herpes simplex virus (human herpesvirus-1, HSV-1) virion and its DNA is reviewed. DNA, proteins, glycoproteins, polyamines, and lipids are currently recognized as the major components of the virion. The protein:DNA ratio for purified HSV-1 is 10.70 ± 0.97, the molecular wt of viral DNA is 10^8 and the wt of virion proteins is 19.4 x 10^{-6} gm/particle. Polyacrylamide gel electrophoresis of purified HSV-1 virions reveals the presence of at least 33 species of polypeptides greater than 25,000 in molecular wt; the major differences in the electrophoretic profiles of various strains of HSV-1 DNA at 99 + 5 x 10^8. Background studies in the repetitive regions in the DNA are summarized; recent studies on the nature and organization of the repetitive regions are discussed in detail. Examination of DNA denatured with formamide and allowed to renature yields two kinds of structures, i.e., DNAs with single small loops with short double-stranded regions and DNAs with barbell structures. Precise localization of the observed cyclodome and its relationship to the termini is inferred from the partial denaturation maps presented and discussed. Analysis of viral DNA with Hin III and Eco RI restriction enzymes note that all of the HSV-1 and HSV-2 DNAs tested to date yield two sets of fragments, i.e., major and minor fragments. The virus stratin specific gel electrophoretic profiles of the fragments are also presented and discussed. Implications arising from the presence of cyclodomes in the DNA structure are considered, and a model of the molecular organization of the DNA is constructed. A detailed analysis of the molecular weight and molar ratios of the HinIII

ragments from HSV-1 shows six major fragments and even or eight minor components; the six major ragments account for 55% of the total genetic nformation. A preliminary map for all of the inIII fragments is then presented, and current nformation on the topology of structural components s diagrammatically represented. Results of various tudies indicate that the DNA appears to be incororated into the virion core, and that the major lycoproteins are on the surface of the virion. 23 references)

014 RELATION OF HERPES SIMPLEX VIRUS TYPE 2 INFECTION TO CERVICAL NEOPLASIA. (Eng.)
osey, W. E. (Emory Univ. Sch. Medicine, Atlanta, a.); Nahmias, A. J.; Naib, Z. M. *Prog. Gynecol.* :541-557; 1975.

he historical development of the herpesvirus-ervical cancer theory is outlined, and the reults of various clinical and epidemiological tudies are summarized. A possible causal relaion of herpesvirus infection to cervical cancer as initially suspected when women with cytoloically detected herpetic cervicitis were observed have an increased rate of cervical neoplasia. additional hypothesis that venereally acquired erpesvirus infection may be causally related to ervical carcinoma has been supported by epidemilogical studies. Studies have demonstrated that e cervix is a major site of infection; most hereic cervical lesions are located at or near the quamocolumnar junction. A correlation of antidy studies with clinical findings suggests that revious exposure to herpes simplex virus type 1 sually modifies the clinical response to herpes mplex virus type 2 (HSV-2). The prevalence of enital herpes varies in different population roups, depending on the extent of sexual promisity. Cytopathological studies have indicated at the sequential cellular alterations vary acrding to the stage of infection. In a study of women with cytologically detectable herpes, 15% d histologically confirmed neoplastic changes. seroepidemiological study revealed that 83% of men with invasive carcinoma, 70% with carcinoma *situ*, and 56% with dysplasia had evidence of ior HSV-2 infections. In a study of young (21 or less) women with cervical carcinoma *in situ*, mean incubation period of four years was found. her studies have indicated that women with HSV-2 tibodies in their sera have a 2-fold increased sk of developing cervical dysplasia and an 8-ld increased risk of carcinoma *in situ*. Although fectious viruses are generally not detectable in rvical neoplastic tissues, HSV-2 antigens are und *via* anticomplement immunofluorescence. A A fragment of HSV-2 has also been detected in man invasive cervical carcinoma. A causal retion of sexually acquired HSV-2 infection to cercal neoplasia is supported by these studies. 2 references)

15 VIRAL LEUKAEMIA IN DOMESTIC CATS. (Eng.)
Bennett, A. M. (Dept. Veterinary Pathogy, Univ. Sydney, Sydney, N.S.W. 2006, Australia); bine, M. *Med. J. Aust.* 2(2):52-62; 1975.

Clinical, cytological, and epidemiological studies of feline viral leukemia are reviewed. A 5-yr survey revealed that 33% of feline malignant diseases are hematopoietic, covering a broad spectrum. The great majority are lymphosarcoma. Although the presenting signs are vague and nonspecific, the major tumor predilection sites are the kidney, anterior thymus, intestine, and mesenteric lymph nodes. Granulocytic leukemia, eosinophilic leukemia, erythremic myelosis, and erythroleukemia are described in the cat. Transmission of feline leukemias into neonatal kittens *via* inoculations of cell free tumor extract, purified virus, cellular tumor extract, and homogenized tumor tissue have been reported. Detailed ultrastructural studies have revealed a wide distribution of C-type particles in infected cats. Further studies have indicated that feline leukemia virus (FeLV) is capable of inducing malignant change in all cell types of the hematopoietic system. The antigenic structure of FeLV corresponds to that of other C-type leukoviruses. Type- or strain-specific antigenic determinants are present on the viral envelope, group-specific antigenic components, and an RNA-directed DNA polymerase have also been isolated. Cells infected with FeLV develop an antigenic determinant on their surface membrane. Antibodies to the envelope and group-specific antigens and to the viral polymerase have also been detected in sera of normal and leukemia cats. A correlation between antibody titer against the cell membrane antigens and resistance to the virus-induced neoplasms has been suggested as having a role of depressed cellular immune responses. Epidemiological and serological surveys have supported a horizontal mode of viral transmission, as the virus has been isolated from urine, saliva, nasal, and tracheal epithelium of infected cats. Preliminary findings have also indicated vertical transmission. However, no correlation between feline viral leukemia and human leukemia is found. (56 references)

3016 MAREK'S DISEASE AND AVIAN LEUKOSIS. (Eng.)
Biggs, P. M. (Houghton Poultry Res. Station, Houghton, Cambs. PE17 2DA, England). *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 166-175.

The pathogenesis, virology, natural history, and control of Marek's disease (MD) and of avian leukosis are reviewed. Although the herpesvirus of MD is ubiquitous among poultry populations, mortality varies from 0 to 80% of a flock. Two forms of MD are recognized; the classical form is characterized by neural involvement, while the main manifestation of the acute form is lymphoid neoplasia. Pathogenesis studies have described three phases of the development of lesions of MD: cytolytic infection, proliferative changes, and chronic inflammation. The development of the pathological changes in the disease is summarized, and observations note that infection is persistent and nonproductive in many cells. Various theories are proposed concerning the cause of the widespread proliferation of lymphoid tissue in MD; intrinsic

theories suggest that the stimulus comes from within the cells while extrinsic theories propose a stimulus outside the cell. Virology studies divide MD viruses into three groups on the basis of their pathogenicity, i.e., those that produce the acute form of MD, those producing the classical form, and those that are apathogenic. While virus is always horizontally transmitted, usually early in life, such infection does not necessarily result in clinical MD. Factors affecting the development of the disease may include: the genetic constitution of the chicken, the sex, the age at infection, the immune status of the host, and the strain(s) of the virus. Although the mechanism of the protection is unknown, an attenuated pathogenic strain and an apathogenic strain of MD virus are shown to immunize chickens against later challenge. The leukoses, caused by a group of RNA tumor viruses called the avian leukosis/sarcoma group, consist of several clearly recognizable pathological entities; lymphoid leukosis is especially noted. The avian leukosis/-sarcoma group of viruses is defined by the presence of group-specific antigens present in the core; however, the viruses are usually classified into subgroups on the basis of properties of the viral envelope: (1) intraspecies host range, (2) interference, (3) antigenic characteristics in neutralization tests. Resistance and susceptibility to the viruses are determined by properties of the host cell membrane. Both vertical and horizontal transmission of leukosis viruses occurs, and a cycle of infection is postulated. The chicken's phenotype, the presence of maternally-derived antibody, plus other undetermined factors may affect the infection and development of the disease. Thus, although the DNA Marek's disease herpesvirus and the RNA leukosis viruses are ubiquitous infections in poultry populations, the development of disease is the exception rather than the rule. (64 references)

3017 STUDIES OF VIRAL GENE PRODUCTS IN CELLS INFECTED OR TRANSFORMED WITH PAPOVA VIRUS. (Eng.) Cuzin, F. (Centre de Biochimie, Universite de Nice, Nice, France). *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 199-206.

The purification and functional identification of the virus gene products of cells transformed or lytically infected by polyoma virus and simian virus 40 (SV40) are reviewed. Viral coded proteins belong to two main classes: the early gene products are the first to be synthesized during the virus cycle, independently of viral DNA synthesis; the late gene products are synthesized only after initiation of viral DNA synthesis and primarily include the structural proteins of the virions. Methodologies employed in current studies include: the purification of the early viral T antigen, the *in vitro* synthesis of viral peptides in viral DNA or mRNA-directed protein synthesizing systems, and the purely analytical identification of the new peptides present in a virus-infected cell. Infection of either permissive or non-permissive cells with polyoma or SV40 leads to derepression of the synthesis of a number of cellular enzymes; therefore, a major problem is that of distinguishing the actual virus coded proteins from the induced cellular ones. The gel electrophoresis analysis of new peptides made in SV40 or polyoma virus-infected cells is then described. Immunological methods offer specific probes for the determination of new products or structures present in virus-infected or transformed cells; a whole series of such changes are designated, i.e., as T, U, S, TSTA, and V antigens. Studies on the nature of the "Tumor" (T) antigen are especially discussed. This antigen has been evidenced *via* complement fixation and immunofluorescence, and is present in the nuclei of transformed or lytically-infected permissive cells; further observations lead to the hypothesis that an early virus coded peptide, product of the temperature sensitive (ts) a gene, carries the T antigenic state. Although T antigen purification by direct immunoadsorption leads to important experimental difficulties, use of a complement fixation assay yields a partial purification of SV40 and polyoma T antigen. The partially purified T antigen has a molecular wt of 60-100,000 daltons, can strongly bind double stranded DNA, and is found in cell extracts under several different forms. The existence of two independent early gene products, in polyoma or SV40, is suggested but not proven. Meanwhile, several hypotheses regarding the function of the early viral protein(s) are presented; these models are derived from *in vivo* studies of ts mutants. The products of the A gene of SV40 and of the ts-a gene of polyoma are suggested to play the role of initiator for the viral replicon. A study of the phenotype of the polyoma ts-a mutant led to the hypothesis that the corresponding gene product is necessary for the integration of viral DNA into the cell genome. It is also suggested that the T antigen is necessary for the maintenance of the transformed state. Analysis of the structural components of the virus particle reveals similar patterns for polyoma and SV40. (45 references)

3018 GENE FUNCTIONS OF SIMIAN VIRUS 40. (Eng.) Kimura, G. (Tottori Univ. Sch. Medicine, Yonago 683, Japan). *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 214-219.

A physical map of the simian virus 40 (SV40) genome is described, the behavior of temperature-sensitive (ts) mutants of SV40 in permissive cells is reviewed, and data on the transforming functions of SV40 is summarized. More than 200 mutants of SV40 thermosensitive for viral replication in permissive cells have been isolated and characterized. These are divided into three complementation groups, i.e., groups A, B, and C or groups I, II, and III; a non-complementing D group and an abnormally-complementing BC group are also known. By using bacterial restrictive endonucleases, a physical cleavage map of the SV40 chromosome, the ts and deletion mutants, was

:onstructed. The ts mutants of the complementation ;roup A or III are considered the early mutants. 'he A mutants are defective in initiation but not ›ropagation or completion of each round of viral)NA replication; furthermore, the A mutation appears .o control the synthesis of a 100,000 dalton pro- :ein suggested to be the precursor of T antigen. 'irus particles from B (I) and C (II) group mutants .re heat labile, suggesting a defect in one or ›ore of the capsid proteins. Temperature shift xperiments show that the ts step in a group II ›utant begins to be completed at 10 hr before the ppearance of new infectious virion, whereas the s reaction of group I occurs in a very late stage f the infectious cycle. Mapping experiments indi- ate that the B and C mutants map in the same seg- ent of the late region in the cleavage map. Whereas mutants cannot "uncoat" at the restrictive temper- ture (40 C), the D gene product is suggested to e a virion protein. Studies of the transforming unctions of SV40 ts mutants show that mutants of roups I and II transform 3Y1 cells at the restric- ive temperature, implying that the function of tructural protein(s) is not involved in the estab- ishment of transformation. Thus, the B and C unctions do not appear required for the maintenance, s well as for the initiation of transformation. he initiation reaction is a more heat labile event han the maintenance reaction(s), implying that he two reactions are dissociable events. Indepen- ent experiments also show that the function of the ene A is required for the maintenance of trans- ›rmation. A model of viral/host interaction is ›ggested. The model is consistent with the notion hat the oncogenicity of the virus is correlated ith its ability to induce cellular DNA synthesis; t also predicts that the majority of the observed roperties associated with the transformed state re not the primary transforming function. (51 eferences)

)19 CEA, AFP AND OTHER POTENTIAL TUMOR MARKERS. (Eng.) Zamcheck, N. (Boston City Hosp., ›ston, Mass.); Pusztaszeri, G. *CA* 25(4):204-214; 975.

.inical studies of the value of carcinoembryonic ›tigen (CEA) and α_1-fetoprotein (AFP) as tumor ›rkers are reviewed. In colon cancer, the CEA ›say is a better indicator of widespread disease, ›rticularly of metastases to the liver, than it is early cancer. A preoperative negative assay (nor- ›l 2.5 ng/ml) does not exclude the diagnosis of can- r, but makes the diagnosis of metastases less like- . In patients with known colon cancer, a negative eoperative CEA assay suggests, but does not guaran- e, a localized lesion and a favorable prognosis. tectable CEA levels are found in a higher percen- ge of patients with left colon cancers than in ose with right colon cancers. Limitations to the e of CEA as a screening test are the normal cir- lating CEA values found in a high proportion of tients with early colon cancer and the nonspeci- city of the assay for cancer of the colon or di- stive tract. Among common benign disorders, CEA vels may be high in severe alcoholic cirrhosis or alcoholic pancreatitis. In serial pre- and postoperative determinations, negative CEA levels do not preclude primary, metastatic, or recurrent colon cancer. Serial determinations are useful in monitoring the response of patients with metastatic breast cancer to chemotherapy; the CEA assay may also be a valuable prognostic marker in lung cancer patients treated by resection and/or radio- and chemotherapy. Serum AFP levels may exceed 1,000 ng/ml in patients with primary liver carcinoma, and serial determinations may help to assess prognosis and recurrence in these patients. The role of AFP as a monitor of chemotherapy has not been adequately studied. Other tumor markers discussed include α_2-H fetoprotein, found in 60% of patients with primary liver carcinoma, 50% of patients with various malignant diseases, and 20-30% of those with benign diseases; β-S fetoprotein, present in 48% of patients with primary liver carcinoma; and fetal sulfoglycoprotein, found in gastric juice of 75 of 78 patients with gastric carcinoma. Two other markers under investigation are carcinoplacental alkaline phosphatase, a nonspecific marker, and an oncofetal antigen that has been found in the sera of patients with carcinoma of the pancreas. (68 references).

3020 PATHOLOGICAL CONSIDERATIONS IN PITUITARY TUMORS. (Eng.) Bergland, R. M. (M. S. Hershey Medical Center, Pennsylvania State Univ., Hershey, Pa. 17033). *Prog. Neurol. Surg.* 6:62-94; 1975.

The histological, immunohistochemical, and light and electron microscopic observations of numerous pituitary tumors and pituitary capsules are reviewed. The early descriptions of pituitary cells and the early histological classifications by acidic-basic stains are presented. Problems of histochemical classifications of pituitary cell types are discussed; these problems include the misleading nature of target organ ablation, the biochemical species specificity of the pituitary trophic hormones, various technical problems, and the tangled nomenclature employed. A functional classification designating pituitary cells according to the hormones elaborated is then presented. Peculiar histological features of the human pituitary include the lack of the pars intermedia, the follicular cells, the posterior pituitary basophils, and the controversial "amphophils." The employment of electron microscopy in the study of pituitary cell types has revealed the vascular relationships, has demonstrated the morphology and packaging of pituitary hormones, and has revealed the lysosomes of prolactin cells and the presence of follicular cells. The use of horseradish peroxidase as a histochemical marker in electron microscopy is described, and a schematic illustration of the Nahane horseradish peroxidase immunohistochemical staining technique is presented. The early history of the use of acidic-basic stains in the classification of pituitary tumors has reported the histological descriptions of chromophobic tumors, acromegaly, and Cushing's disease. Subsequent operative histological observations, and problems in the evaluation of pituitary tumor histology, are discussed

in detail. The Young series of 44 consecutive pituitary tumors associated with acromegaly, the histological results of the Schelin series of ten acromegalic patients, and the Ray series analyzing exenterated sellae in 55 acromegalic patients are described. Discrepancies between autopsy studies and operative studies are noted. Further electron microscopic observations, radioimmune assays of pituitary hormones, and immunohistochemical analyses of pituitary tumors are also discussed. Following a description of the normal microvascular structure of the pituitary, the tumor-pituitary interface (pseudocapsule), tumor-sellar interface (pseudocapsule) and tumor-brain interface (capsule) are described and diagrammatically and photographically represented. Studies of the vascular supply of pituitary tumors note the structure and importance of the normal pituitary portal system, illustrate the blood supply of experimental tumors, and suggest that human pituitary tumors may likewise derive their blood supply wholly *via* the pituitary portal system. (32 references)

3021 PROGRESS IN THE CLASSIFICATION OF LYMPHOID AND/OR MONOCYTOID LEUKEMIAS AND OF LYMPHO AND RETICULOSARCOMAS (NON-HODGKIN'S LYMPHOMAS). (Eng.) Mathé, G. (Institut de Cancerologie et d'Immunogénétique (INSERM et Association Claude Bernard), Hôpital Paul-Brousse, 14-16, avenue Paul-Vaillant Couturier, 94800 Villejuif, France); Belpomme, D.; Dantchev, D.; Pouillart, P. *Biomedecine* 22(3):177-185; 1975.

The construction of a new classification of lymphoid and monocytoid leukemias and hematosarcomas and new analytical methods are reviewed. A discussion of classical and new morphological and immunological methods emphasizes the value of immunological markers, ultrastructural analysis by conventional and scanning electron microscopy, and Giemsa smears. Non-thymic-dependent (B) lymphocytes have been found in chronic lymphoid leukemia, primary macroglobulinemia, and chronic macroglobulinemic proplasmocytic leukemia. The B nature of myleoma plasma cells is also evident in plasma-cell leukemia and heavy chain diseases. The thymic-dependent (T) cells of Sézary's disease and traditional acute lymphoid leukemia are discussed. A fifth type of T or B cells have been noted in immunoblastic acute lymphoid leukemia and leukemic lymphosarcoma. Difficulties in the classification of malignant histiocytosis and in the identification of chronic or subacute leukemias as lymphoid *versus* monocytoid are also acknowledged. The classification of hematosarcomas notes the B lymphoid cells of the nodular lymphosarcoma and the T or B lymphoid cells of the diffuse lymphosarcoma. Nodular lymphosarcomas are recognized as prolymphocytic or lymphoblastic, while diffuse lymphosarcomas may be prolymphocytic, lymphoblastic, or immunoblastic. True (African) Burkitt's lymphosarcomas are distinguished from pseudo (non-African) Burkitt's lymphosarcomas on the basis of macrophages and Epstein Barr virus genome. The mediastinal form of lymphosarcoma is composed of T immunoblasts, and the cells of mycosis fungoides are considered as T lymphocytes. The diagnosis of reticulosarcoma is based on the presence of many reticulin fibers at histiological examination and on the cytological aspect of the cells on smears. All the prognostic parameters in the four types of common acute lymphoid leukemia are seen to be related to cytological type, and a revision of the nomenclature and classification of the disease is considered justified. (62 references)

3022 CURRENT AND FUTURE CONCEPTS OF LUNG CANCER. (Eng.) Benfield, J. R. (Harbor General Hosp., 1000 Carson St., Torrance, Calif. 90509); Pilch, Y. H.; Rigler, L. G.; Selecky, P. *Ann. Intern. Med.* 83(1):93-106; 1975.

Diagnosis and therapeutic advances in the treatment of lung cancer, and the objectives of future research are discussed. An understanding of the natural history of lung carcinoma is important; several detailed case studies are presented. Serial roentgenograms, have been useful in many retrospective diagnoses. Survival is a function of many variables; these include cell type, anatomic location, tumor size, and patient performance status. As an aid to reporting and discerning the prognosis, a staging system is described; such staging also contributes to determining surgical resectability. Diagnostic methods including bronchoscopy, mediastinoscopy, scalene node biopsy, percutaneous needle biopsy, aspiration needle biopsy, and bronchial brush biopsy are evaluated. Various screening procedures for the detection of lung cancer are reviewed. Such screenings involve chest roentgenograms, sputum cytology, and combined roentgenograms and cytology. Concepts of operative care are discussed, with particular attention to lobectomy and pneumonectomy. The role of radiotherapy in the management of lung carcinoma, including combined chemotherapy-radiation therapy approaches, is discussed and followed by a discussion of potential immunotherapy. The prognostic significance of delayed cutaneous hypersensitivity reactions is considered, and previous studies of immunotherapy are evaluated. (80 references)

3023 SARCOMAS OF THE LARYNX. (Eng.) Friedmann, I. (Northwick Park Hosp., Watford Road, Harrow, Middlesex, England, HA1 3UJ). *Can. J. Otolaryngol.* 4(2):297-302; 1975.

The epidemiology and histological features of benign mesenchymatous tumors, leiomyosarcomas, cartilaginous tumors, rhabdomyosarcomas, Kaposi's hemangiosarcomas, and giant cell sarcomas of the larnyx are reviewed. The benign tumors of the larynx (e.g., polyps, granulomas, and cysts) are not true neoplasms and arise in the stroma of the vocal cord. Diagnostic difficulties may arise when the stroma shows enhanced cellularity, and the surface epithelium is hyperplastic. Sarcomas of the larynx occur once to every 100 cases of carcinoma, more than 50% of these tumors being fibrosarcomas. Most fibrosarcomas occur in men over 50 yr of age, although they may occur at any age and in either sex. Histologically, fibrosarcomas in the larynx resemble fibrosarcomas in other parts of the body and are divided into well differentiated and poorly

differentiated types; the former has a better prognosis. Leiomyosarcoma of the larynx is extremely rare. Cartilaginous tumors of the larynx include chondromas, osteochondromas, and low and higher grade chondrosarcomas. These tumors form lobules surrounded by loose connective tissue; the larger tumors expand into the soft tissue of the larynx, esophagus, or trachea. Low grade chondrosarcomas are characterized by a variation in nuclear size and shape, and extensive clustering of chondrocytes. Plump binucleated cells may be frequent, and scattered giant cells have been seen in recurrences. Rhabdomyosarcomas are highly malignant neoplasms of the striated muscle, and about 80% of those in the head and neck occur in children under 12 yr of age. The following histological types are recognized: embryonal, sarcoma, nonstriated embryonal rhabdomyosarcoma and striated embryonal rhabdomyosarcoma, and alveolar rhabdomyosarcoma. The diagnosis is often difficult. Kaposi's hemangiosarcoma is a rare neoplasm characterized by a simultaneous proliferation of vasoformative tissue and spindle cells. Fibrous trabeculae are formed, giving the lesion a lobulated appearance. Giant cell sarcoma is also a rare occurrence. A concerted study of laryngeal tumors might reveal that they are more common than the number of published cases would suggest. (19 references)

3024 CLUSTERING OF CANCER. (Eng.) Pike, M. C. (Univ. Southern California Sch. Medicine, Los Angeles, Calif.); Henderson, B. E. *CA* 25(4): 230-234; 1975.

Clustering of cases of Hodgkin's disease and leukemia was studied to determine if such clusters occur more often than one would expect purely by chance and would, therefore, be an indication of a contageous process. The standard test of clustering considers each possible pair of patients and records all those with cancers that occurred within a specified time and distance. This method has two flaws: (1) it assumes that patients living close together had direct or indirect contact; and (2) it presumes that both the latent period of the disease and the time interval between clinical onset and diagnosis are short and relatively constant. It is suggested that the case-control method of statistical analysis with detailed interviewing of both groups would give more valid results and would demonstrate whether cases had more contact at a relevant time than did controls. In one case-control study in Albany, 31 of 208 patients diagnosed as having Hodgkin's disease from 1950 to 1970 were linked. There were nine instances of possible case-case spread and 25 possibilities of case-contact-case transmission. Another case-control study involving 97 patients was recently completed in Oxford, England. Initial analysis indicates a considerable number of links between patients, but no more so than among controls. Other interview studies with inadequate control groups have been reported, but are of little scientific value. Many studies of clusters of childhood leukemia cases have been performed using the time-space interaction method. These efforts have resulted either in negative findings or in weak positive results. It is suggested that the issue of clustering in leukemia remains open, not because there are a sufficient number of positive results, but because the phenomenon has only been studied superficially. It is concluded that there is no significant evidence that any human cancer has the characteristics of a communicable disease. (22 references)

3025 EPIDEMIOLOGY OF HODGKIN'S DISEASE: GEOGRAPHIC VARIATIONS IN INCIDENCE AND HISTOLOGIC SUBTYPES. (Eng.) Sacks, M. I. (Hadassah Univ. Hosp., Jerusalem, Israel). *Proc. Int. Cancer Congr. 11th.* Vol. 6 (*Tumors of Specific Sites*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 345-350.

Recent studies in which pathologists from different parts of the world have reviewed pathological material from their countries have confirmed raw cancer registry data indicating that there are considerable geographic variations in the incidence and age distribution of Hodgkin's disease (HD). There are marked geographic differences in the relative frequency of the nodular sclerosis subtype HD and it seems most unlikely that these are merely due to the use of different histologic criteria by pathologists in different countries. A major determinant of the geographic differences in the epidemiologic and histologic patterns of HD seems to be the socioeconomic level of the community studied. Poor socioeconomic conditions seem to lead to HD at an earlier age, and to a predominance of the histologic types associated with a poor prognosis. In poorer countries, nodular sclerosis is uncommon at all ages, which may be a reflection of host resistance. These findings are consistent with the view that the pattern of HD seen in a particular population is the result of an interaction between the etiologic agent(s) of the disease and host susceptibility. According to this view, the different epidemiologic and histologic patterns of HD reflect different types of host response in different environments rather than multiple disease entities. While host susceptibility is probably largely dependent on environmental influences, the possibility that genetic factors may also play a role cannot be excluded and it has recently been suggested that the histologic picture of HD may be influenced by the HL-A phenotype of the host. Having accepted the evidence that environmental factors are important in the etiology of HD, the great challenge is to further elucidate the possible role of infective agents in the causation of the disease. (34 references)

3026 STATISTICS AND CANCER. (Eng.) Mould, R. F. (Westminster Hosp., Page Street Wing, London SW1, England). *Nurs. Times* 71(29):1122-1133; 1975.

The statistical analyses of cancer incidences, survival times, mortality rates, and cure rates are

discussed. Survival time from treatment to death can be divided into two periods: apparent disease-free time (remission) and terminal disease time (time from recurrence to death). The distribution of terminal disease time for 854 cervical carcinoma patients is graphically represented. The prognosis differs with the clinical stage, but the terminal disease time is approximately independent of clinical stage. The survival time distribution of patients who eventually die with primary and/or metastatic stage three breast carcinoma, stage two cervix carcinoma, and pharyngeal carcinoma is also graphically represented; similar trends are noted in all three sections. Based on a series of 99 recorded patient histories, the random site distribution of second primaries subsequent to cervical cancer is illustrated. The necessary parameters required for a cancer registry data bank are tabulated. Wide variations have been found in the national patterns of cancer incidence throughout the world. The annual incidence rate and annual mortality rate are defined and cancer incidence rates are graphed. The unusual incidence and national registration patterns of cervical carcinoma *in situ* are discussed. Examples of both occupational and nonoccupational environmental links with cancer are tabulated. The recognition of and precaution for the occupational hazard associated with X-rays and radium is noted. Wide variations in national cancer mortality rates are also noted, and the annual mortality rates from 1851 to 1969 are discussed. National patterns of cancer mortality, and 1969 mortality rates for cancer and other diseases are tabulated; different rates in men and women are revealed. Computations and methods of calculating five-year survival rates are described, and five-year cancer survival rates are also tabulated. A discussion of the concept of "cure rate" indicates that the five-year survival rate will not always be a good indication of cure. Crude and age-corrected survival rates are analyzed, and estimates of the proportion cured are made using statistical prediction models. It is concluded that the definitive year is usually about the 10th yr after treatment. (No references)

3027 GROWTH OF PERMANENT LYMPHOID CELL CULTURES FROM HUMAN SOURCE: TENTH ANNIVERSARY. (Eng.)

Wang, C. -H. (Univ. Texas System Cancer Center, Houston, Tex. 77025); Sinkovics*, J. G.; Kay, H. D.; Gyorkey, F.; Shullenberger, C. C.
Tex. Rep. Biol. Med. 33(1):213-250; 1975.

The development and peculiar features of human lymphoid cell cultures are reviewed, and previously unpublished observations on 52 permanent lymphoid cell cultures are presented. The techniques of growing permanent cultures of human lymphoid cells from WBC, bone marrow explants, splenic tissue, and lymph node tissue are described. The events of lymphoblastoid transformation in tissue cultures of lymph nodes or spleen derived from malignant lymphomas of Hodgkin's disease are tabulated; the duration of elongated cells in cultures undergoing lymphoblastoid transformation is compared with cultures failing to produce lymphoid cells. Established cultures of lymphoid cells show morphological features displaying a wide range of developmental stages (i.e., reticulum cells, monocytes or macrophages, lymphoblasts, plasmablasts, and large and small lymphocytes). Generally stable diploid, hyperdiploid, or hypodiploid chromosome ranges have been found, although abnormal karyotypes have also been observed. The kinetics of growth and cloning are discussed and the production of well-defined antigens, immune globulins, and various mediators of the delayed hypersensitivity reaction is documented. The inhibition of the growth of established target cells by permanent cell lines of lymphoid cells is graphically represented. Other studies have been concerned with the roles of the Epstein Barr virus in the establishment of permanent human lymphoid cell lines; herpesvirus morphology has been found in lymphoid cells established from explants of breast carcinoma, angiosarcoma, Kaposi's sarcoma, malignant melanoma, and thyroid carcinoma. The pathogenicity of human lymphoid cell lines in animals is discussed, and their apparent infinite growth potential *in vitro* has been noted. Lymphoid cell cultures are also obtained from normal healthy individuals and from patients with numerous pathological conditions, including malignant lymphomas, leukemias, nasopharyngeal carcinoma, Chediak-Higashi syndrome, and multiple myeloma. Exceptional cell lines developed from patients with lymphoproliferative diseases and exceptionally uniform suspension cultures of lymphoblastoid cells are discussed in detail. New applications of lymphoid cell cultures in immunology are then described. The reaction of human sera with established lymphoid cell lines may indicate an expression of antibody activity directed to the Epstein Barr virus or its antigens; established lymphoid cell lines express cytotoxicity indiscriminately to batteries of target cells, and suspension cultures of human lymphoid cells can be used as target cells in assays measuring migration inhibitory factors. The major paradox thus appears to be the morphological and functional heterogeneity of the cultures. (150 references)

3028 CARCINOEMBRYONIC ANTIGEN (CEA): MOLECULAR BIOLOGY AND CLINICAL SIGNIFICANCE. (Eng.)

Fuks, A. (Montreal Gen. Hosp., Canada); Banjo, C.; Shuster, J.; Freedman, S.O.; Gold, P. *Biochim. Biophys. Acta* 417(2):123-152; 1975.

Information on the carcinoembryonic antigen (CEA) of the human digestive system is discussed. Tumor-specific antigens in experimentally-induced animal tumors, as well as the induction of experimental animal tumors by chemical carcinogenic agents, DNA or RNA oncogenic viruses, and human tumor antigens, are reviewed. Technique for the demonstration of CEA, including the use of antisera and immunochemical procedures, are noted. This is followed by a description of the known cellular localization of the CEA, the cellular and human responses to CEA, and observations on the circulation and metabolism of CEA. The initial experimental work on CEA summarized establishes the existance of a material associated with carcinomata originating from the entodermally-derived portion of the gastrointestinal

act and with certain fetal tissues. A radioimmuno-
say measurement of CEA activity is subsequently
scussed. A report on purification techniques of
A preceeds a description of physical properties.
ese include molecular weight, molecular charge,
d miscellaneous parameters including solubility
d stability. An analysis of structure includes
formation on the carbohydrate composition; the
ructure of the carbohydrate moiety is determined
a acid hydrolysis of CEA, periodate oxidation and
zymatic hydrolysis; the latter process utilizes
uraminidase, galactosidase, galactose oxidase,
ycosidases, and the non-specific protease nagase.
e amino acid composition of CEA is noted, as are
me details of the primary structures of the protein
iety and the nature of the carbohydrate-protein
nkage. Immunochemical studies include binding
udies between ^{125} I-CEA and various antisera, inter-
tions between CEA and specific lectins, comparative
nibition studies in the ^{125} I-CEA-anti-CEA system
d cross-reactivity studies. Studies on the nature
the tumor-specific grouping of the CEA molecule,
addition to information on the nature of the cir-
lating substance(s) measured by radioimmunoassay,
e discussed. The application of quantitative assays
r CEA to clinical medicine is discussed, including
e significance of the range of positivity, the im-
ct of false-positive assays, and the potential pre-
ctive diagnostic value in cancer diagnosis. Fur-
er data indicate the value of the assay in the
rveillance of cancer patients, including the
termination of disease progression and the moni-
ring of the effectiveness of chemotherapy. Factors
at await resolution include the chemical structure
the tumor-associated site, the biologic role of
A in cellular homeostasis and its relationship to
e process of malignant transformations. (143 re-
ences)

29 THE PRESENT STATE OF BIOCHEMICAL RESEARCH ON CHALONES. (Eng.) Thornley, A. L.
p. Zool., Birkbeck Coll., Univ. London, England);
rence, E. B. *Int. J. Biochem.* 6(5):313-320; 1975.

eview is presented of some of the biochemical
racteristics of chalones. The striking biologi-
characteristics of chalones include: (1) they
produced in the host tissue; (2) they inhibit
otic activity *in vivo* and *in vitro;* (3) their
ion is reversible; and (4) they are not species
class-specific. They act at the G1 and/or G2
se of cell cycle but DNA synthesis may not be
ediately stopped. They are small polypeptides
h or without carbohydrate moieties. Several
es of chalones are discussed. Epidermal G2
lone (molecular weight 30,000-40,000) is a glyco-
tein potentiated by adrenaline. Epidermal G1
lone (molecular weight 10,000-20,000) is also a
coprotein that acts at pre-S phase and is resis-
t to RNase, trypsin and pronase. RBC G1, fibro-
st G1, and granulocyte G1 chalones were also men-
ned briefly. The RBC and granulocyte chalones
te in the same zone on Sephadex G-75. The exis-
ce of a liver chalone waits confirmation. The
sibility of chalone (molecular weight 30,000-
000) specific to T and B lymphocytes is discussed.
elanocyte G1 chalone has been isolated from Hard-
ing-Passey melanoma consisting of RNA and protein,
and is augmented by hydrocortisone. The "antichal-
ones" may have reactive sites separate from mitotic
stimulators, but the actual sites are unknown. In
melanocyte and lymphocyte G1 chalones, a sialic acid
component is necessary for conserving activity.
There is no positive correlation between cyclic AMP
levels and chalone action. Chalones do act by re-
stricting the nucleoside pool in cultured lympho-
cytes, with an inhibition of nucleoside kinase acti-
vity. Melanocyte G1 chalone depresses both protein
and DNA synthesis. Chalones may be useful in cancer
treatment as adjuncts to chemotherapy. However, the
immunological responses have not been distinguished
from the mitotic activity, and they may play only a
part of the complex of tissue-stimulators and inhi-
bitors. (45 references)

3030 THE ROLE OF CHOLESTERYL 14-METHYLHEXADE-CANOATE IN GENE EXPRESSION AND ITS SIGNIFICANCE FOR CANCER. (Eng.) Hradec, J. (Dept. Biochemistry, Oncological Inst., 18000 Prague 8, Czechoslovakia). *Prog. Biochem. Pharmacol.* 10:197-226; 1975.

The role of cholesteryl 14-methylhexadecanoate (CMH) in enzyme activation, gene expression, and malignant growth is discussed. Experimental results indicate that lipids are involved in the synthesis of the aminoacyl-tRNA complex. CMH, the only lipid found to be active in that respect, forms part of the molecule of amino acid-tRNA-ligase required for normal enzymatic activity. Experiments suggesting a close relationship between the chemical structure and biological activity of CMH indicate the presence of a fatty acid with a definite chain-length, and anteiso-type branching is essential for the activity in protein synthesis. CMH administration also enhances the rate of DNA-dependent RNA polymerase activity, and increases the specific activity of the ribosome finding enzyme (transferase I). The presence of CMH has thus been found to be essential for the normal function of amino acid-tRNA ligases, transferase I, transferase II, and peptidyl transferase. Studies on ribosomes indicate that CMH affects the function of the A site and the peptidyl transferase site. Preliminary isolation experiments have revealed higher quantities of CMH in tumor tissues than in other animal tissues. Despite a relatively large variability, the duration of individual periods of decreased or increased CMH levels are strictly dependent on the tumor growth rate. Further results indicate that tumor growth is accompanied by significant changes in CMH metabolism, although no qualitative differences in mechanisms of gene expression for normal and tumor cells have yet been found. While it is assumed that all tissues demand a constant supply of CMH, it is suggested that CMH affects the regulation of protein synthesis and the growth of malignant tissues. (71 references).

3031 THE ROLE OF DNA REPAIR AND SOMATIC MUTATION IN CARCINOGENESIS. (Eng.) Trosko, J. E. (Dept. Human Development, Michigan State Univ., East Lansing, Mich.); Chu, E. H. Y. *Adv. Cancer Res.* 21:391-425; 1975.

Information on the role of DNA repair and somatic mutation in carcinogenesis is reviewed. A highly speculative and heuristic scheme that has been developed to account for a wide range of observations that make it appear that the carcinogenic process has several heritable components is described. Based on the assumptions (a) that germ-line mutations on several levels can influence carcinogenesis, and (b) that DNA repair and somatic mutagenesis are related in mammalian systems in a manner similar to bacteriological systems, a model linking genetic and environmental factors influencing DNA repair with observations on the initiation and promotion of tumors is presented. Within this model, genes that influence (a) the level of genetic damage, (b) the level and efficiency of the repair of DNA damage, and (c) the proliferation of the altered cells, are those that are subject to wide variation in expression owing to individual genetic or environmental predispositions. At this time, only circumstantial evidence links DNA repair to carcinogenesis in human beings. A critical component of the somatic mutation theory of cancer will be an elaboration of the role of the repair of carcinogen-induced DNA damage to mutagenesis in eukaryotic systems. Within the framework of the model presented, it appears that the goal of a total prevention of cancer and the development of a universal therapy for the cure of cancer will be extremely difficult, if not impossible, to attain. Even if the amount of potential carcinogens (initiators) in the human environment could be prevented from increasing, it could never be reduced to zero levels. There are many steps at which genetic variability could lead to the genetic predisposition to cancer, as well as many levels by which certain environmental factors can enhance the carcinogenic and aging processes. Genetic instability, due to faulty DNA repair (or replication) on the gene or chromosomal level in the germ cells, has selective advantage because it can contribute to sources of variation needed for the evolution of the species. At the same time, it is hypothesized that gene and chromosome instability in the soma can manifest themselves in both the carcinogenic and aging process. In essence, a cybernetic-feedback type of model has been advanced that links germ-line mutations, which favor the initiation and promotion of somatic mutations, to those somatic mutations that alter a cell's ability to respond to cell division regulators. (212 references)

3032 A CRITICAL EVALUATION OF THE METHODS USED FOR DETERMINING CARCINOGENICITY. (Eng.) Weisburger, E. K. (Natl. Cancer Inst., Bethesda, Md.). *J. Clin. Pharmacol.* 15(1):5-15; 1975.

In the selection of a bioassay method to determine the carcinogenicity or long-term toxicity of a drug, consideration should be given to the chemical structure of the test compound and its physical and chemical properties. Other factors that influence test results are: route of administration, dosage and frequency of exposure, the age of the animal at the start of the test, the species, strain, sex, diet, test duration, immune status, the possible presence of synergists or inhibitors and even the solvent or vehicle used for administration of the test substance. Guidelines for selecting the route of administration are summarized together with the bioassay procedure used at the National Cancer Institute and results of tests with chemotherapeutic agents. Present NCI protocols call for 50 animals of each sex and species to be tested at each of at least two dose levels. At the end of the experimental and/or holding period, preferably at least two yr for rats and 18-20 months for mice, experimental animals and controls are killed for histopathologic study. Cyclophosphamide (three i.p. injections/week for six months) had a weak but definite carcinogenic effect on the lung and bladder in Swiss-Webster mice and the breast in Sprague-Dawley rats. Female mice given azathioprine had a significant incidence of lymphosarcomas, while the number of lung tumors in male mice and s.c. tumors in male and female rats was also higher than normal. Methotrexate resulted in a slight increase in lymphosarcomas in male and female mice. It is concluded that these drugs should be prescribed only when the disease cannot be controlled by less toxic drugs. (76 references)

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3071 EPIDEMIOLOGICAL ASPECTS OF CHORIOCARCINOMA. (Eng.) Anonymous. *Br. Med. J.* 3(5984):606-607; 1975. (15 references)

3072 STUDIES OF LEUKEMIA CELL PROLIFERATION. (Eng.) Mauer, A. M. (Children's Hosp., Cincinnati, Ohio 45229): Lampkin, B. C. In: *Reviews in Leukaemia and Lymphoma, 1--Advances in Acute Leukaemia* edited by Cleton, F. J.; Crowther, D.; Malpas, J. S. Amsterdam, North Holland Publishing Co., 1974, pp. 69-94. (119 references)

3073 CANCER: A SECOND OPINION. (Eng.) Issels, J. (No affiliation given). Hodder and Stoughton, 1975, 216 pp.

3074 CHEMICAL STUDY CENTER FOR PHARMACEUTICAL DRUGS AND BIOLOGICALLY ACTIVE PRODUCTS, PADOVA: SCIENTIFIC ACTIVITY IN THE YEAR 1973. (Ita.) Rodighiero, G. (Centre di studio sulla chimica del farmaco e dei prodotti biologicamente attivi, Padova, Italy). *Ric. Sci.* 44(4):584-588; 1974. (23 references)

)75 HISTOCHEMISTRY OF GAMMA-GLUTAMYL TRANSPEPTIDASE IN RAT LIVER DURING AFLATOXIN B_1-DUCED CARCINOGENESIS. (Eng.) Kalengayi, M. M. R. aboratorium voor Histochemie en Cytochemie, Departnt Medische Navorsing, Fakulteit Geneeskunde, Kathieke Universiteit Leuven, 12 Minderbroedersstraat, 3000 Leuven, Belgium); Ronchi, G.; Desmet, V. J. *Natl. Cancer Inst.* 55(3):579-588; 1975.

e histochemical changes of γ-glutamyl transpeptise (γ-GTase) in the livers of rats treated with latoxin B_1 (AFB_1) were studied. Thirty-six male star rats were given, by gastric intubation, small ses of aflatoxin B_1 (AFB_1): 50 μg twice weekly for ur weeks and then 75 μg twice weekly for ten weeks. eir livers were examined histologically and histoemically for γ-GTase. Before 15 wk no significant patic lesions and no changes in γ-GTase activity re detected. From 15 wk, hyperplastic liver cell ci appeared. Composed of either clear vacuolated, perbasophilic, or eosinophilic liver cells, they ogressively increased in number and size. Regardss of their morphologic differences, they all owed a strong γ-GTase activity localized on the ll membranes and in the cytoplasm. From 44 wk, rcinomas developed in 69% of the animals; they were edominantly well differentiated hepatocellular turs and, to a lesser extent, hepatocholangiocellular rcinomas. Independent of histologic features, the ors disclosed a markedly increased γ-GTase actiy both on tumor cell membranes and in the cytoism. During all preneoplastic and neoplastic ges, no γ-GTase activity was seen in the parenma surrounding hyperplastic foci and carcinomas. trong γ-GTase activity in hyperplastic foci and sequently in hepatocarcinomas further supported commonly assumed precancerous nature of the for- and illustrated the return of the latter to a e embryonic biochemical state. The fact that the al reappearance of γ-GTase occurred before the elopment of true carcinomas and then persisted in tumor tissue indicates a close link between ene reappearance and neoplastic transformation, but s not clarify whether this was pathogenetic in the plastic process.

6 INTERACTION OF AFLATOXIN B_1 WITH DNA. (Eng.) imoto, S. (Dep. Biochem., Fac. Sci., Univ. Kanazawa, an); Ohba, Y. *J. Biochem.* 77(1):187-195; 1975.

interaction of aflatoxin B_1 ($A-B_1$) with native and t-denatured calf thymus DNA is described. With ive DNA, the absorption spectrum of $A-B_1$ underwent ift in the region of 300-420 nm, with an isobestic nt at 376 nm. Alkaline hydrolysis of the DNA-bound proceeded more readily than that of the free in, and the hydrolyzed product was more labile. sociation of the complex was easily accomplished eat and by increased ionic strength (0.1 M NaCl), the DNA released from the complex was shown to ouble stranded. With heat-denatured DNA, $A-B_1$ ed a complex with an isobestic point at 380 nm. e this complex was stable in 0.1 M NaCl, it is sidered that the mechanism of binding is different that with native DNA. Based on Scatchard plots, as calculated that one toxin molecule was bound each 80-140 nucleotide moiety of native DNA. The number of binding sites was doubled in the presence of calf thymus histones. The mechanism of the interaction remains unknown, but presumably intercalation is not involved.

3077 BINDING OF [^{14}C]AFLATOXIN B_1 TO CELLULAR MACROMOLECULES IN THE RAT AND HAMSTER. (Eng.) Garner, R. C. (Dept. of Experimental Pathology and Cancer Res., Univ. of Leeds, 171 Woodhouse Lane, Leeds LS2 3AR, England); Wright, C. M. *Chem. Biol. Interact.* 11(2):123-131; 1975.

The uptake and binding of ring-labeled [^{14}C]aflatoxin B_1 (AFB_1) by rat and hamster liver and kidney was studied. Male Wistar rats or male Golden Syrian hamsters were injected ip with 40 μg/100 g [^{14}C]AFB_1 in dimethylsulphoxide (40 μg AFB_1/0.1 ml). Three animals were used to measure uptake and binding of the compound for each time period. DNA was estimated by the diphenylamine reaction using calf-thymus DNA as standard; rRNA was estimated by the orcinol reaction using yeast tRNA as standard and protein was determined by the Lowry-Folin procedure, using bovine serum albumin as standard. Binding of the carcinogen to nucleic acids was far greater than that to protein. Rat liver DNA bound ten times and ribosomal (rRNA) 20 times more carcinogen than protein. There were also differences in the amount of carcinogen bound to rat liver nucleic acids compared to those of the hamster, the latter species binding lower amounts of the carcinogen. Rat liver DNA bound four times and rRNA ten times as much AFB_1 six hr after carcinogen administration, whereas liver protein-bound AFB_1 was similar for the two species. Whereas rat liver nucleic acid-bound carcinogen decayed with time, no such fall was seen in the hamster; this remained at a low level throughout the 48-hr period. In contrast, reaction of the carcinogen with kidney macromolecules was similar for the two species. The much higher binding of AFB_1 to nucleic acids than to protein might account for the potent carcinogenicity of this compound in the rat, particularly since liver binding does not differ between a susceptible and a resistant species. Another factor in carcinogenic sensitivity may be the removal of nucleic acid-bound radioactivity with time, a possible repair process.

3078 EFFECT OF LIFETIME EXPOSURE TO AFLATOXIN B_1 IN RATS. (Eng.) Ward, J. M. (Natl. Cancer Inst., Bethesda, Md.); Sontag, J. M.; Weisburger, E. K.; Brown, C. A. *J. Natl. Cancer Inst.* 55(1):107-113; 1975.

Studies were conducted to determine the effects of exposure of rats to transplacental and milk metabolites of aflatoxin B_1 (AFB_1) followed by lifetime dietary exposure. AFB_1 was fed at 2 ppm to a group of pregnant F344 rats from the time of conception; it was then fed to their offspring until death. For comparison, the same diet was administered to another group of rats beginning at age 6-7 wk. The survival time of male rats was significantly shorter than that of the female rats of both groups. However, the survival times of rats of the same sex in both groups did not differ significantly. The major causes of death were hepatic neoplasms with metastases, al-

though some early deaths occurred before neoplasms developed. Most deaths were from malignant hemorrhagic liver tumors, histologically diagnosed as hemangiosarcomas, which caused rupture and hemorrhage into the peritoneal cavity or metastases to the lungs. These hemangiosarcomas were readily transplantable and did not produce α-fetoprotein. Ultrastructurally, they were composed of poorly differentiated cells resembling endothelial cells. Nodules of hyperplasia induced by aflatoxin B_1 sometimes grew large (>1.5 cm), and two were transplanted. Colon tumors developed in more than 20% of rats exposed *in utero* as well as in those given AFB_1 from six or seven weeks of age. A few rats had tumors of the kidney, oral cavity, and hematopoietic system. These findings indicate that AFB_1 should be considered a possible etiologic agent for colon cancer. Inhibition of the hepatocarcinogenic effect of AFB_1 may induce colon and/or renal tumors.

3079 A POSSIBLE PROTECTIVE ROLE FOR REDUCED GLUTATHIONE IN AFLATOXIN B_1 TOXICITY: EFFECT OF PRETREATMENT OF RATS WITH PHENOBARBITAL AND 3-METHYLCHOLANTHRENE ON AFLATOXIN TOXICITY. (Eng.) Mgbodile, M. U. K. (Vanderbilt Univ. Sch. Medicine, Nashville, Tenn. 37232); Holscher, M.; Neal*, R. A. *Toxicol. Appl. Pharmacol.* 34(1):128-142; 1975.

The possibility of a protective role for reduced glutathione (GSH) in aflatoxin B_1-induced hepatotoxicity in male Sprague-Dawley rats was investigated. A 200-mg/kg dose of cysteine (a gluthathione precursor), given ip prior to the administration of aflatoxin B_1 (3 mg/kg), reduced the hepatic necrosis and partially reversed the decrease in the activity of the hepatic drug metabolizing enzyme system seen on administration of the same dose of aflatoxin B_1 alone. In contrast, diethyl maleate (0.2 or 0.6 ml/kg), given ip two hours prior to the aflatoxin, enhanced the aflatoxin-induced hepatotoxicity. In contrast to untreated rats, pretreatment with phenobarbital (80 mg/kg, ip, daily for three days) appeared to block the liver necrosis and the decrease in mixed function oxidase activity seen on administration of aflatoxin B_1. On the other hand, pretreatment of the rats with 3-methylcholanthrene (20 mg/kg, ip, daily for three days; or one 20 mg/kg dose 72 hr before aflatoxin) did not protect against the hepatic damage or the decrease in the activity of benzphetamine *N*-demethylase seen on administration of aflatoxin B_1. The results suggest that glutathione may be involved in reducing the toxicity of aflatoxin B_1 to the liver.

3080 BIOCHEMICAL AND MORPHOLOGICAL CHANGES IN HEPATIC NUCLEAR MEMBRANES PRODUCED BY *N*-HYDROXY-2-ACETYLAMINOFLUORENE. (Eng.) Glazer, R. I. (Dept. Pharmacology, Emory Univ., Atlanta, Ga. 30322); La Via, M. F. *Cancer Res.* 35(9):2511-2519; 1975.

The effect of *N*-hydroxy-2-acetylaminofluorene (N-OH-AAF) on the ultrastructure and synthesis of hepatic nuclear membranes was evaluated in partially hepatectomized (male Sprague Dawley) rats. The incorporation of L-[4,5-^{3}H]leucine into two nuclear membrane fractions increased within two hours after hepatic resection and reached the maximum, 200% of the control, at 20 hr. After partial hepatectomy, the decay of radioactivity in nuclear membrane proteins revealed similar half-lives (30-38 hr) for the two membrane fractions compared to those from sham-operated animals. The protein concentration of the nuclear membrane fraction of higher density decreased sharply within two hours after partial hepatectomy (4 μg/g compared to 16 μg/g for sham-operated rats). This level remained low for 20 hr; 6.6 μg protein/g were found at 40 hr. Electrophoresis of both nuclear membrane fractions showed a similar composition. Nine proteins were resolved, varying from 21,000-190,000 daltons. The two major protein bands were in the range of 50,000 and 70,000 daltons, respectively. Treatment of partially hepatectomized animals with N-OH-AAF caused marked dilation of the nuclear envelope and rough endoplasmic reticulum *in situ*. Vacuolization and evagination of the perinuclear membranes were also found in isolated nuclei obtained from carcinogen-treated rats. Inhibition by N-OH-AAF of the incorporation of L-[4,5-^{3}H]leucine into the nuclear membranes was dose-dependent and remained depressed throughout a 60-min labeling period. These results suggest that the inhibitory effects on RNA and protein synthesis, previously shown to be produced by this hepatocarcinogen, lead to disruption of the morphology and synthesis of the nuclear envelope.

3081 NONSPECIFIC INHIBITION OF DNA REPAIR SYNTHESIS BY TUMOR PROMOTERS IN HUMAN DIPLOID FIBROBLASTS DAMAGED WITH *N*-ACETOXY-2-ACETYLAMINOFLUORENE. (Eng.) Poirier, M. C. (Natl Cancer Inst., Bethesda, Md.); De Cicco, B. T.; Lieberman, M. W. *Cancer Res.* 35(6):1392-1397; 1975.

The effects of tumor-promoting croton oil, 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and phenol, and their nonpromoting analogs (phorbol, 1,8-dihydroxyanthraquinone, and 4-nitrophenol) on DNA repair synthesis were examined in human diploid fibroblasts (Wl-38) damaged by N-acetoxy-2-acetylaminofluorene. At concentrations of 0.001, 0.01, and 0.05%, croton oil inhibited DNA repair and replicative synthesis; anthralin (10 and 100 M) and TPA (10 and 50 M) inhibited this synthesis. The nonpromoting analogs of the chemical had little effect. Phenol inhibited replication by over 50% at 10^3 μM, and inhibited DNA repair synthesis by 50% at 10^3 μM. Its analog, 4-nitrophenol, completely inhibited both processes at 10^3 μM. To investigate the specificity of this phenomenon, the effects of these agents on DNA-replicative synthesis, RNA synthesis, protein synthesis, and cell morphology were evaluated. At equimolar concentrations, tumor promoters inhibited DNA replicative synthesis, as effectively as repair synthesis. RNA and protein synthesis were similarly inhibited over the same range of concentrations. Extensive morphological changes, interpreted as evidence of toxicity, were seen at concentrations of promotors that inhibited the macromolecular syntheses studied. The non-promoting analogs, with the exception of nitrophenol, had little effect

n these processes and showed only slight morphologi-al damage. Thus, tumor-promoting agents produce a oncerted inhibition of a number of macromolecular ynthetic processes, including DNA repair synthesis. t inhibitory concentrations there is morphological vidence of cellular injury. These findings suggest hat the effects of promoters on DNA repair synthe-is are nonspecific, and that it is unlikely that lterations in repair synthesis alone account for heir mechanism of action in tumor promotion.

082 COMPARATIVE EFFECTS OF STRAIN, SPECIES, AND SEX ON THE ACYLTRANSFERASE- AND SULFOTRANS-ERASE-CATALYZED ACTIVATIONS OF *N*-HYDROXY-*N*-2-FLUO-ENYLACETAMIDE. (Eng.) King, C. M. (Michael Reese ed. Cent., Chicago, Ill.); Olive, C. W. *Cancer Res.* 5(4):906-912; 1975.

e capacities of tissues from different species to tivate arylhydroxamic acid acyltransferase (an en-me which promotes the introduction of arylamine roups into nucleic acids) were investigated and com-ared. The enzyme was found evenly distributed from e glandular stomach to the distal portion of the lon in Sprague-Dawley, Fischer, Buffalo, and Wistar ts, Swiss mice, Syrian golden hamsters, Camm/Hartley inea pigs, and New Zealand rabbits. Enzyme activity s also analyzed in Stumptail macaque monkey, mon-el dog, and goat tissues. No consistent differences acyltransferase activities of the liver, kidney, ain, or spleen of Sprague-Dawley and Fischer rats re found. The activity was demonstrable in the li-rs of guinea pigs, hamsters, rabbits, and monkeys; the kidneys, stomach, and colon of guinea pigs and msters; in the small intestine of guinea pigs, ham-ers, rabbits, and monkeys; and in the lungs of ham-ers. Mouse, goat, and dog tissues were essentially void of activity. The ability of liver extracts 05,000 x *g* supernatants) from F_1 hybrids of Sprague-wley and Fischer rats to carry out the transforma-on of *N*-hydroxy-*N*-2-fluorenylacetamide into a re-tive species by conjugation with sulfate was inter-diate between those of the same sex of the two pa-ntal strains. The author suggests that the eluci-tion of the role of this enzyme in the carcinogenic ocess could be facilitated by associating the enzyme th a particular type of cell within a tissue.

83 ALTERATIONS IN MICROSOMAL METABOLISM OF BENZO[*a*]PYRENE IN MICE FED BUTYLATED DROXYANISOLE. (Eng.) Speier, J. L. (Dept. Lab. dicine and Pathology, Univ. Minnesota, Minneapolis, nn. 55455); Wattenberg, L. W. *J. Natl. Cancer st.* 55(2):469-472; 1975.

metabolism of benzo[*a*]pyrene (BP) by liver micro-nes in female A/HeJ mice fed a control diet or a et containing butylated hydroxyanisole (BHA) was udied. Forty mice were fed 5 mg/g BHA in the diet two weeks. Aryl hydrocarbon hydroxylase activity H) was not changed by BHA feeding. However, the surement of other parameters demonstrated that feeding altered the microsomal system metabolizing Incubation of BP and calf thymus DNA with liver rosomes from BHA-fed mice showed about half the binding of BP metabolites to DNA as compared to that of controls. The AHH activity of mice fed BHA was much more sensitive to *in vitro* inhibition by α-naphthoflavone (0.16, 0.32, or 0.64 μM) than that of controls. The amount of cytochrome P450 was increased per unit weight of microsomal protein and liver in mice fed BHA. The ethyl isocyanide binding spectra were measured to see if alterations of cytochrome P450 might be produced by BHA feeding. The maximum at 430 nm was the same in control and BHA-fed mice. However, the maximum at 455 nm was lower in BHA-fed mice than in controls, which indicated that BHA had caused some change. The data show that BHA feeding results in altered properties of liver microsomes, including a decrease in BP metabolite binding to DNA.

3084 INHIBITION OF BENZO(*a*)PYRENE METABOLISM CATALYZED BY MOUSE AND HAMSTER LUNG MICRO-SOMES. (Eng.) Hill, D. L. (Kettering-Meyer Lab., Southern Res. Inst., Birmingham, Ala. 35205); Shih, T.-W. *Cancer Res.* 35(10):2717-2723; 1975.

Microsomal enzymes that metabolize benzo(*a*)pyrene in mouse and hamster lungs were characterized, and their inhibition by various agents was studied. Benzo(*a*)pyrene hydroxylase activity was induced in female DBA/2 mice and Syrian golden hamsters by giving them injections of 3 or 9 mg benz(*a*)anthra-cene, respectively, 16 hr before they were sacri-ficed. Induced and constitutive microsomal enzymes of mouse and hamster lungs catalyzed both the hy-droxylation of benzo(*a*)pyrene and reactions that led to its irreversible binding to macromolecules. For mouse and hamster, the induced lung hydroxy-lases had K_m values of 1.10 and 0.52 μM, respec-tively. The induced hydroxylases were strongly inhibited by 7,8-benzoflavone (0.25 and 50 μM) and were stimulated by cyclohexene oxide (2 mM). For-mation of the macromolecular product by the induced "binding" enzyme followed Michaelis-Menten kinetics, except for substrate inhibition, and had K_m values of 0.52 and 0.25 μM for lung microsomes from mouse and hamster, respectively. These reactions were also inhibited by 7,8-benzoflavone (50 μM). The reaction catalyzed by the constitutive hydroxylase of mouse lungs was characterized by a brief lag period, but it proceeded in a linear fashion after the lag. The enzyme required 60 μM benzo(*a*)pyrene to achieve maximum reaction velocity. Above this concentration, strong substrate inhibition was ob-served; accurate values for V_{max} and K_m could not be derived. The constitutive hydroxylases were moderately inhibited by butylated hydroxytoluene (50 μM), retinol (50 μM), cyclohexene oxide (2 mM), and 7,8-benzoflavone (50 μM). The product of the constitutive "binding" enzyme formed in a reaction that followed Michaelis-Menten kinetics. The K_m value for enzymes from mouse and hamster lungs were 11.8 and 4.9 μM, respectively. Formation of this product was strongly inhibited by butylated hydrox-ytoluene and by retinol but not strongly by 7,8-benzoflavone or cyclohexene oxide. Since other evidence indicates that a constitutive enzyme may be involved in carcinogenesis by benzo(*a*)pyrene, and since this reaction is inhibited by two known

anticarcinogens, it is suggested that it may be involved in this process.

3085 POSITION-SPECIFIC OXYGENATION OF BENZO[*a*]-PYRENE BY DIFFERENT FORMS OF PURIFIED CYTOCHROME *P*-450 FROM RABBIT LIVER. (Eng.) Wiebel, F. J. (Natl. Cancer Inst., Bethesda, Md. 20014); Selkirk, J. K.; Gelboin, H. V.; Haugen, D. A.; van der Hoeven, T. A.; Coon, M. J. *Proc. Natl. Acad. Sci, USA* 72(10):3917-3920; 1975.

Oxygenated products of benzo[*a*]pyrene formed in a reconstituted microsomal mixed-function oxidase system containing cytochrome *P*-450 (*P*-450LM), phospholipid, and NADPH-cytochrome *P*-450 reductase (NADPH:ferricytochrome oxidoreductase) were detected by high-pressure liquid chromatography. Three cytochrome fractions purified from hepatic microsomes from phenobarbital-treated rabbits, were studied; the various forms of the cytochrome are designated by their relative electrophoretic mobilities. The total benzo[*a*]pyrene oxygenation rate was greatest for *P*-450LM$_{1,7}$, intermediate for *P*-450LM$_2$, and least for *P*-450LM$_4$. The phenolic products were eluted in two peaks, A and B, that contained primarily 9-hydroxy- and 3-hydroxybenzo[*a*]pyrene, respectively. The ratio of peak A to peak B phenols was 0.11 for *P*-450LM$_2$ and 0.45 for *P*-450LM$_4$. Thus, the relative amounts of the various phenols formed by these two cytochrome fractions differ markedly. The positional specificity of the hydroxylation is also indicated by large differences in the fluorescence spectra of the phenolic products formed by the two cytochromes. *P*-450LM$_2$ and *P*-450LM$_4$ did not form benzo[*a*]pyrene dihydrodiols, thereby showing that benzo[*a*]pyrene oxide hydratase activity was absent from these purified preparations. Ninety percent of the phenols formed by *P*-450LM$_{1,7}$ were eluted in peak B; the metabolites produced by this preparation also included dihydrodiols, thus indicating the presence of hydratase activity. The positional specificities of different forms of cytochrome *P*-450 may channel polycyclic aromatic hydrocarbon metabolism into the various activation and detoxification pathways and thereby help determine the cytotoxic and carcinogenic activity of these compounds.

3086 EFFECT OF *CAPSELLA BURSA-PASTORIS* ON LIVER CATALASE ACTIVITY IN RATS FED 3'-METHYL-4-(DIMETHYLAMINO)AZOBENZENE. (Eng.) Kuroda, K. (Res. Inst. for Chemobiodynamics, Chiba Univ., Izumi-cho 3-9-1, Narashino 275, Japan); Akao, M. *Gann* 66(4): 461-462; 1975.

The effect of *Capsella bursa-pastoris* extract on the liver catalase activity in male Donryu rats treated with an azo dye hepatocarcinogen was studied. Catalase activity was determined by the titanyl sulfate method in three groups of rats: rats fed a diet containing 0.06% 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB, 0.5 g) and then given water containing 0.2% of *Capsella bursa-pastoris* extract; rats given 3'-Me-DAB and untreated drinking water; and rats given neither 3'-Me-DAB nor the herb extract. Catalase activity was expressed by the value of reaction constant, *K*, obtained from an equation taking into account reaction time, initial substrate concentration, and residual substrate concentration. Liver catalase activity was considerably reduced in rats given 3'-Me-DAB and ordinary drinking water (536 *K*/100 mg liver protein), compared with the activity (820 *K*/100 mg protein) in untreated controls. Administration of the herb extract after ingestion of 3'-Me-DAB prevented the reduction of liver catalase activity (activity of 826 *K*/100 mg protein in extract-treated rats). This finding is in agreement with histopathologic observations showing that the herb extract prevented the induction of hepatomas in rats fed 3'-Me-DAB.

3087 DEVELOPMENT OF HEPATOCELLULAR CARCINOMAS IN RATS TREATED WITH BENZENE HEXACHLORIDE. (Eng.) Ito, N. (Nagoya City Univ., Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-Ku, Nagoya 467, Japan); Nagasaki, H.; Aoe, H.; Sugihara, S.; Miyata, Y.; Arai, M.; Shirai, T. *J. Natl. Cancer Inst.* 54(3): 801-805; 1975.

The effects of prolonged po administration of the α-, β-, γ-, and δ-isomers of benzene hexachloride (BHC) on rat liver were examined histologically. Well-differentiated hepatocellular carcinomas were observed in the liver of male W rats fed a basal diet containing 1,500 or 1,000 ppm of α-BHC for 72 wk. Many typical nodular hyperplasias developed in all groups given 1,500 or 1,000 ppm α-BHC. No neoplastic changes or other abnormal findings, such as oval cell infiltration, fatty changes, fibrosis, or bile duct proliferation of the liver, were observed in groups receiving 500 ppm α-, β-, γ-, or δ-BHC. Unlike many other hepatocarcinogens, BHC (1,500 or 1,000 ppm) caused slight oval cell infiltration or bile duct proliferation in non-neoplastic areas, and other changes were not as marked as with other hepatocarcinogens. This suggests that the mechanisms of the carcinogenic effects of organochlorides differ from those of other hepatocarcinogens.

3088 STUDIES ON THE INTERACTION OF SAFROLE WITH RAT HEPATIC MICROSOMES. (Eng.) Elcombe, C. R. (Dept. Biochemistry, Univ. Surrey, Guildford, England); Bridges, J. W.; Gray, T. J. B.; Nimmo-Smith, R. H.; Netter, K. J. *Biochem. Pharmacol.* 24(15):1427-1433; 1975.

The interaction of 4-allyl-1,2-methylenedioxybenzene (safrole) with rat hepatic microsomes was investigated using spectrophotometry. Phenobarbital-stimulated microsomes were obtained from male Sprague-Dawley rats after they had been given ip injections of sodium phenobarbital (80 mg/kg) daily for three days prior to sacrifice. Safrole-stimulated microsomes were obtained from rats fed safrole (2% wt/wt) in the diet for two weeks before sacrifice. On reduction with NADH, NADPH or $Na_2S_2O_4$, microsomes from safrole-pretreated rats showed characteristic absorption maxima at 427 and 455 nm. The same spectrum was obtained after incubation *in vitro* of control and phenobarbital-stimulated microsomes with safrole (0-833 μM), NADPH (60 μM) and oxygen. Sub-

quent addition of carbon monoxide to microsomes of frole-pretreated rats causes an absorption maxi- n at 448 nm, characteristic of the 3-methylchol- threne type of induction of microsomal hydroxylase otein. The suspected cytochrome P-450-safrole tabolite complex, which can be visualized only in reduced state of cytochrome P-450, was very able; this was demonstrated by its preservation rough the preparation procedure for microsomes or er dialysis or detergent treatment. However, when frole or ethylbenzene was added, both absorption tima decreased in a time-dependent manner. This uld be measured for each time point after complete luction of the microsomal preparation by adding S_2O_4. It is concluded that safrole leads to the synthesis of a 3-methylcholanthrene type cytochrome 50 and formation of a safrole metabolite-cytochrome 50 complex, which in turn can be cleaved *in vitro* safrole or other lipophilic compounds.

9 FACTORS MODULATING BENZIDINE CARCINOGENICITY BIOASSAY. (Eng.) Vesselinovitch, D. (Pritzker Sch. Medicine, Univ. Chicago, Chica- Ill. 60637); Rao, K. V. N.; Mihailovich, N. *Can- Res.* 35(10):2814-2819; 1975.

an integrated series of studies, several factors e assessed for their capability to influence the come of carinogenicity of benzidine dihydrochlo- e in C57BL/6J x C3HeB/FeJ F_1 mice of both sexes. nals were either 6 or 1 wk of age at the begin- g of treatment. Six-week-old mice were exposed po administration of carcinogen delivered either food (50 or 100 ppm daily) or by stomach intuba- n at equivalent dose levels at twice-weekly in- vals. In addition, a 150-ppm dose level in food administered for 39, 54, or 84 wk. A limited ee-wk, daily intubation of benzidine (30 or 100 nouse) was also explored in 1- and 6-wk-old mice. nals were killed in all studies at 90 wk of age, their tumor incidence was evaluated. Depending experimental conditions, benzidine treatment ef- ted development of liver tumors, lung adenomas, lerian gland cystadenomas, and lymphoreticular plasms. Continuous feeding of adult mice for 84 t three dose levels of benzidine resulted in de- pment of liver tumors with a positive dose-re- se relationship in both sexes. The analysis of revealed a greater susceptibility of females of males (94% *versus* 44% at 150 ppm). Twice- ly administration of benzidine by stomach intu- on was less hepatocarcinogenic than continuous ing of equivalent amounts. In the series in h male mice were fed food containing 150 ppm of idine for only 34 or 54 wk, in contrast to the e 84-wk schedule, a negative relationship was rved between the incidence of liver tumors and duration of treatment. Daily administration of g of benzidine to infants by stomach intubation a three-wk period significantly enhanced devel- nt of liver tumors only in males (66%). Intro- ion of 150 ppm of benzidine into food offered to er and offspring from delivery to weaning led to lopment of liver tumors in 95% of male mice and % of females. No liver tumors developed follow- similar three-week treatment of six-week-old a- s. The data indicate the necessity of considering the modifying role of age, sex, duration of treatment, dose of carcinogen, and nonspecific toxicity of the agent when selecting a bioassay system for evaluation of carcinogenicity.

3090 *IN VITRO* TRANSFORMATION OF BHK21 CELLS GROWN IN THE PRESENCE OF CALCIUM CHROMATE. (Eng.) Fradkin, A. (Health Sci. Cent., State Univ. New York Stony Brook); Janoff, A.; Lane, B. P.; Kuschner, M. *Cancer Res.* 35(4):1058-1063; 1975.

BHK21 cells were grown in the presence of calcium chromate ($CaCrO_4 \cdot 2H_2O$) to detect any *in vitro* transformational changes in morphology and growth behavior due to carcinogenic stimuli. BHK21 cells treated with chromium were cultured in Dulbecco's medium with 10% calf serum, penicillin and streptomycin. Plastic tissue cultures were rinsed with phosphate-buffered saline, sodium phosphate buffer and NaCl, followed by trypsinization in 0.1% trypsin. Control (C) and chromate-treated (CT) groups were maintained in tetraplicate to observe reproducibility in changes of morphology and growth induced by chromate ions. CT subgroups were grown in chromate salt (CT-H) followed by introduction of chromate-containing medium added to the culture. Random C cells and CT cells were grown in methocel according to the method of Stoker with modified amounts of chromate added to the CT cells growing in methocel. *In vitro* transformation of BHK21 cells grown in the presence of $CaCrO_4$ revealed alterations in morphology and cell growth when exposed to medium containing 0.25 and 0.5 μg/ml of $CaCrO_4$. Treated cells were shortened and randomly oriented and had enlarged nuclei and granular cytoplasm. Cells grown in methocel treated with chromate underwent many cell divisions to form clusters while normal cells reproduced more slowly under the same growth conditions. These alterations were found to be irreversible and persisted for long periods of time. Transformation due to $CaCrO_4$ was found to be directly related to the concentration of the chromium salt. The results suggest that $CaCrO_4$ does cause *in vitro* transformation in BHK21 cells. Further investigation into *in vivo* transformation by $CaCrO_4$ and other ions is indicated.

3091 ENHANCED HEPATOTOXICITY OF CARBON TETRACHLORIDE, THIOACETAMIDE, AND DIMETHYLNITROSAMINE BY PRETREATMENT OF RATS WITH ETHANOL AND SOME COMPARISONS WITH POTENTIATION BY ISOPROPANOL. (Eng.) Maling, H. M. (Natl. Heart and Lung Inst., Bethesda, Md. 20014); Stripp, B.; Sipes, I. G.; Highman, B.; Saul, W.; Williams, M. A. *Toxicol. Appl. Pharmacol.* 33(2):291-308; 1975.

Elevated plasma glutamic-pyruvic transaminase (GPT) activity induced by carbon tetrachloride (CCl_4), thioacetamide, or dimethylnitrosamine in male Sprague-Dawley rats was increased by pretreatment with four doses (each 5 ml/kg) of ethanol administered po 48, 42, 24, and 18 hr before the hepatotoxic agent. Blood ethanol concentrations were less than 5 mg/100 ml when a hepatotoxic agent was injected ip. Pretreatment with ethanol did not affect the hepatic concentrations of CCl_4 or its metabolite, chloroform ($CHCl_3$), at one hr after ad-

ministration of CCl_4. The CCl_4-induced diene conjugation tended to increase after ethanol pretreatment and was significantly potentiated by pretreatment with isopropanol or pyrazole and a single dose of ethanol. In rats pretreated with ethanol, covalent binding of $^{14}CCl_4$ to liver protein and lipid *in vivo* was significantly greater at six and 24 hr than in control rats. The *in vitro* binding of $^{14}CCl_4$, $^{14}CHCl_3$, and $^{14}CBrCl_3$ to hepatic microsomal protein was increased by ethanol pretreatment. Ethanol pretreatment also doubled the *in vitro* rate of demethylation of dimethylnitrosamine by liver microsomes. The similarities in microsomal effects of pretreatment with isopropanol and with ethanol suggest that similar mechanisms are involved in their potentiation of CCl_4-induced hepatotoxicity. The potentiation by pretreatment with ethanol, but not with isopropanol, of the hepatotoxicity of thioacetamide and dimethylnitrosamine suggests that ethanol pretreatment also activates some additional mechanisms.

3092 IS THERE ANY ASSOCIATION BETWEEN ELEVATED SERUM PROLACTIN LEVEL AND MAMMARY ADENOCARCINOMA INDUCED BY 7,12-DIMETHYLBENZ(a)-ANTHRACENE? (Eng.) Feuer, G. (Dept. Clinical Biochemistry, Banting Inst., Room 521, Univ. Toronto, Toronto, Canada M5G 1L5); Kellen, J. A.; Kovacs, K. *Res. Commun. Chem. Pathol. Pharmacol.* 11(3):435-444; 1975.

The association between mammary carcinogenesis induced by 7,12-dimethylbenz(a)anthracene (DMBA) in the rat, the influence by manipulations of its hepatic metabolism, and the secretion of prolactin was investigated. Mammary tumors were induced in female Wistar rats, and the appearance of palpable tumors was assessed twice weekly after the administration of various test compounds. The ability of the liver to metabolize drugs was measured by assay of coumarin 3-hydroxylase activity. Serum prolactin levels were determined using a modified radioimmunoassay. Administration of the following compounds seven days before DMBA treatment and continued for 14 days resulted in elevated serum prolactin: Coumarin (1 mM/kg, po), 4-methylcoumarin, phenobarbital (0.2 mM/kg, ip), and CCl_4 (2.5 mM/kg, two doses only). Only coumarin and 4-methylcoumarin reduced tumor incidence. These observations do not support the assumption that the suppression of DMBA-induced breast adenocarcinoma by coumarin and 4-methylcoumarin is mediated *via* prolactin.

3093 SPECIFIC ESTROGEN BINDING IN RAT MAMMARY TUMORS INDUCED BY 7,12-DIMETHYLBENZ(A) ANTHRACENE. (Eng.) Boylan, E. S. (Univ. Rochester Cancer Cent., N.Y.); Wittliff, J. L. *Cancer Res.* 35(3):506-511; 1975.

The binding of 17β-[^{3}H]estradiol to ovarian-dependent and ovarian-independent 7,12-dimethylbenz(a)-anthracene (DMBA)-induced mammary tumors in Sprague-Dawley rats was studied to determine whether the two classes of tumors differed in this respect. Seven-week-old mice were given DMBA by gastric intubation (25 mg/wk for five weeks), and bilateral ovariectomy was performed within 2-3 wk of the appearance of tumors. Tumors were classified as ovarian-dependent if the tumor mass decreased for a minimum of ten days after ovariectomy, and as ovarian-independent if growth continued for more than ten days after ovariectomy. While all tumors classified as ovarian-dependent had substantial cytoplasmic estrogen-binding capacity, 10 of 13 ovarian-independent tumors had a total binding capacity, a specificity for estrogens, an extent of saturation *in vivo*, and an ability for translocation which were similar to these parameters of the ovarian-dependent tumors. The capacity to bind estrogens in DMBA-induced mammary tumors may indicate that tumor growth may be affected by ovariectomy, but it does not preclude the possibility that some of these tumors will be unaffected by endocrine ablation. The results are similar to those observed among human patients with breast tumors.

3094 INHIBITION OF THE ACUTE TOXICITY AND ADRENOCORTICOLYTIC EFFECT OF 7,12-DIMETHYLBENZ-(a)ANTHRACENE BY ISOPROPYLVALERAMIDE AND ALLYLISOPROPYLACETAMIDE IN THE RAT. (Eng.) Somogyi, A. (Univ. Nebraska Medical Center, Omaha, Nebr. 68105); Levin, W.; Banerjee, S.; Kuntzman, R.; Conney, A. H. *Cancer Res.* 35(9):2500-2505; 1975.

The effects of allylisopropylacetamide (AIA, 12.5-400 mg/kg, ip) and isopropylvaleramide (IVA, 2.50-25.00 mg/kg, ip) on the hemorrhagic adrenocortical necrosis and mortality induced by 7,12-dimethylbenz(a)-anthracene (DMBA, 12 mg/kg, iv, one hour after AIA or IVA administration) were studied in female Sprague-Dawley rats. The effects of secobarbital, aprobarbital, phenobarbital, and pentobarbital (37-46 mg/kg, ip or iv) on DMBA damage were also determined, as was the influence of IVA on the clearance of [^{3}H]-DMBA and its metabolites from the adrenals, liver, and blood and on the *in vitro* metabolism of DMBA and benzo(a)pyrene. In the latter experiments, the amounts of fluorescent phenolic metabolites of benzo-(a)pyrene and DMBA formed by liver homogenates from IVA-treated (10-25 mg/kg) rats were determined. IVA and AIA inhibited the hemorrhagic adrenocortical necrosis caused by DMBA, the anti-DMBA activity of these compounds not being dependent upon the presence of the reactive allyl group in the molecule. Similarly, the four barbiturates tested did not protect against DMBA damage, regardless of whether or not they contained on allyl group. Thus, the protective action of IVA and AIA could not be attributed to the destruction of the microsomal enzyme system responsible for the activation of DMBA. The toxicity of dimethylnitrosamine, another carcinogen that requires metabolic activation by microsomal enzymes, was not influenced by either IVA and AIA. IVA, which counteracted the adrenocorticolytic action of DMBA when given prior to, with, or after the carcinogen, had no discernible effect on hydrocarbon metabolism *in vitro* or *in vivo*. Although the mechanism of action of IVA remains unclear, it might be valuable as a tool in studies of the nonmetabolic aspects of DMBA carcinogenesis.

095 EFFECT OF DIMETHYL SULFOXIDE AND DIMETHYL-FORMAMIDE ON THE GROWTH AND MORPHOLOGY OF MOR CELLS. (Eng.) Borenfreund, E. (Mem. Sloan-ttering Cancer Cent., New York, N.Y.); Steinglass, ; Korngold, G.; Bendich, A. *Ann. NY Acad. Sci.* 3:164-171; 1975.

e effects of dimethylsulfoxide (DMSO, 1-2%), di-thylformamide (DMF, 0.5-1%), and 5-bromodeoxyuri-ne (BrdU, 1-3 μg/ml) on cell morphology were stud-d in growing cultures of QUA tumor, a cell line tablished from a methylcholanthrene-induced tumor C57/B1/6 mice. All three agents induced a drastic ange from the randomly piling, non-contact-inhibi-d growth characteristic of tumor cells to one which re closely resembled the parallel, oriented growth normal cells. The morphological changes were nifest after about three days with DMSO and DMF, d after five to six days with BrdU. Changes could maintained indefinitely in the continuous pre-nce of the agents, but reversal to the original owth patterns resulted after removal of the agents om the medium. Thymidine (but not uridine) pre-nted the BrdU effect at five times the molar con-ntration of BrdU, but did not affect the DMF or SO effect. Dibutyryl cyclic AMP, with or without eophylline, could not induce the reported changes, r could cytochalasin B. Puromycin (0.2 μg/ml), clohexamide (0.05 μg/ml) and ethidium chloride 0^{-7} M) all failed to interfere with the observed fects. Cells grown in the presence of DMSO, DMF BrdU demonstrated a considerable decrease in glutinability with wheat germ lipase and concana-lin A. Surface membrane glycoproteins of cells own in the presence of DMSO or DMF had a decreased gh-molecular weight fucose-containing fraction and increased low-molecular weight fraction, but BrdU eatment did not significantly alter the elution ofile of the glycopeptide fractions of these cells. etreatment of tumor cells with 2% DMSO for 13 days large part prevented the multinucleation caused exposure to cytochalasin B(1 μg/ml) for four days. ither DMSO, DMF, or BrdU significantly altered the take of 2-deoxyglucose by tumor cells. It is sug-sted that DMSO and DMF may exert their effects on llular differentiation and that BrdU may act at gene level.

96 VARIABLE EFFECTS OF A LIPOTROPE-DEFICIENT, HIGH-FAT DIET ON CHEMICAL CARCINOGENESIS RATS. (Eng.) Rogers, A. E. (Dept. Nutrition and d Science, Massachusetts Inst. Technology, Cam-dge, Mass. 02139). *Cancer Res.* 35(9):2469-2474; 5.

lier studies that demonstrated enhanced chemical cinogenesis in the liver, colon, and probably phagus of male Sprague-Dawley rats fed a lipo-pe-deficient, high-fat diet were continued. The sent experiments were designed to examine the ge of the dietary effect on chemical carcino-esis; rats were fed either the marginally lipo-pe-deficient, high-fat diet or an adequate con-l diet, and treated with *N*-2-fluorenylacetamide 02% or 0.0125% in the diet), 3,3 diphenyl-3-ethylcarbamoyl-1-propyne (5-10 mg/wk, 20 wk, ragastrically) *N*-methyl-*N*-nitroso-*N'*-nitroguanidine (10-20 mg/kg/wk, 10 wk, intragastrically), *N*-[4-(5-nitro-2-furyl)-2-thiazoly]formamide (0.188% in diet, 18 wk) aflatoxin G_1 (25 μg/day, 41 days, intragastrically) or ethionine (50-100 mg/kg/wk, 22 wk, intragastrically). *N*-2-Fluorenylacetamide induced hepatocarcinomas more rapidly and in higher incidence (41%) in deficient rats than in control rats (19%). 3,3-Diphenyl-3-dimethylcarbamoyl-1-propyne induced a higher incidence of hepatocarcinomas but not gastric tumors in deficient rats. Aflatoxin B_1, (15 μg/day, 25 days, intragastrically), included as a positive control, was significantly more hepatocarcinogenic in deficient rats (87% incidence in deficient rats *vs* 11% in nondeficient rats). Gastric tumor induction by *N*-methyl-*N*-nitroso-*N'*-nitroguanidine and induction of tumors of the urinary bladder by *N*-[4-(5-nitro-2-furyl)-2-thiazyl-yl]formamide were not influenced by diet. Aflatoxin G_1 and ethionine were toxic to 82% of deficient rats, and carcinogenic doses could not be administered. These results may indicate that deficient dietary levels of the lipotropes and the metabolic load imposed by the high dietary level of fat are responsible for the enhancement of hepatocarcinogenesis.

3097 EFFECTS OF 5,5-DIPHENYLHYDANTOIN AND RELATED CARBAMATES AND HYDROXYLAMINES ON NUCLEIC ACID AND PROTEIN SYNTHESIS OF PROLIFERATING HUMAN LYMPHOCYTES. (Eng.) MacKinney, A. A. (Veteran's Admin. Hosp., Madison, Wis. 53706); Vyas, R. *Toxicol. Appl. Pharmacol.* 33(1):38-45; 1975.

In order to explore the mode of action of 5,5-diphenylhydantoin (DPH), the inhibitory effect of compounds with related hydroxylamine or carbamate structures were studied in the DNA and protein synthesis of normal proliferating human lymphocytes. DNA synthesis was estimated by treating phytohemagglutinin-stimulated lymphocytes with [methyl-^{3}H]-thymidine (0.12 mg/mCi) during the final two hours of incubation. Protein synthesis was estimated by incubating 3-day-old cultures with L[4,5^{3}H]leucine (4.3 mg/mCi). A series of 3-hydroxyhydantoins was weaker than the parent DPH, indicating that the N3 hydroxyl group did not activate the compounds, whereas substitutions at the C5 position generally diminished activity. Parahydroxylation of the benzene ring enhanced inhibition of DNA and protein synthesis. Acetoxylation of the N3 position of diphenylhydantoin greatly increased its potency; acetoxylation of 2-acetylaminofluorene had a similar effect. 1-Acetyl-3-acetoxy-5,5-dephenylhydantoin inhibited DNA synthesis to approximately the same degree as *N*-acetoxy-2-acetyl aminofluorene, xylyl phenyl carbamate, hydroxyurea, and hydroxylamine. This derivative of DPH illustrates the central role of the N3 position in metabolic reactions with lymphocytes. The contribution of this derivative to lymphomagenesis is not known.

3098 ASSOCIATION OF EXOGENOUS ESTROGEN AND ENDOMETRIAL CARCINOMA. (Eng.) Smith, D. C. (Mason Clinic, 1118 9th Ave., Seattle, Wash. 98101); Prentice, R.; Thompson, D. J.; Herrmann, W. L. *N. Engl. J. Med.* 293(23):1164-1167; 1975.

To determine the association between the incidence of endometrial cancer and the use of estrogen in menopausal and post-menopausal women, 317 patients with adenocarcinoma of the endometrium were compared with an equal number of matched controls having other gynecologic neoplasms. One-hundred fifty-two of the patients used estrogen, as compared to 54 of 317 controls. Thus, the risk of endometrial cancer was 4.5 times greater among women exposed to estrogen therapy. When estrogen use was adjusted for concomitant variables such as obesity, hypertension, diabetes, parity, referral pattern, age at diagnosis, year of diagnosis, and other gynecologic neoplasms, the magnitude of the increased relative risk was associated with several of these variables. The risk was highest in patients without obesity and hypertension. Exogenous estrogen therapy is associated with an increased risk of endometrial carcinoma, but this increased relative risk is less apparent in patients with physiologic characteristics previously associated with an increased risk.

3099 HORMONAL STATUS OF BREAST CANCER. II. ABNORMAL URINARY STEROID EXCRETION. (Eng.)
Kodama, M. (Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya, Japan); Kodama, T.; Yoshida, M.; Totania, R.; Aoki, K. *J. Natl. Cancer Inst.* 54(6):1275-1282; 1975.

The urinary excretion of 14 neutral steroids was measured by gas-liquid chromatography in women with early and advanced breast cancer, in women with early uterine cancer, and in healthy women. For statistical analysis, measurements with a skewed distribution were normalized by the square root or logarithmic transformation. Urine samples from patients with neoplasia were taken 3-7 days before and 10-14 days after surgery; samples from controls were taken on the 20th days of the menstrual cycle. Measurements of age-dependent steroids were adjusted to a value of 35 yr of age for the premenopausal group and to 60 yr of age for postmenopausal group. The premenopausal patients with early breast cancer excreted subnormal amounts of five steroids (11-hydroxyandrosterone, 11-hydroxyethiocholanolone, prenanediol, pregnanetriol, and tetrahydrocorticosterone) and increased amounts of tetrahydrocortisol, compared to controls. Postmenopausal breast cancer patients excreted greater amounts of five steroids (one steroid from 17-ketosteroids and four from 17-hydroxycorticoids) that the controls. The discrepancy between premenopausal and postmenopausal breast cancer was tentatively related to ovarian-adrenal dysfunction in the course of aging. Oophorectomy induced a long-lasting tumor regression only in patients with a high value for the ratio of 11-deoxy-17-ketosteroid/17-hydroxycorticosteroid in urine taken before surgery; the ratio in the responsive patients decreased remarkably after surgery. A constitutional change in 17-ketosteroids, as observed in a postmenopausal breast-cancer patient and a premenopausal healthy women of urban origin, favored the geographic importance in the genesis of breast malignancy. 11-Deoxy-17-ketosteroid excretion at the premenopausal stage and the pregnanetriol/tetrahydrocortisone ratio at the postmenopausal stage differentiated breast cancer from uterine cancer. The question of whether these changes are specific for breast cancer and causally related to the malignancy awaits further investigation. Whether premenopausal breast cancer should be distinquished from postmenopausal breast cancer is also questioned.

3100 ANDROGEN RECEPTORS IN THE HUMAN PROSTATE GLAND. (Eng.) Mainwaring, W. I. P. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Milroy, E. J. G. *Proc. Int. Cancer Congr. 11th.* Vol. 5 *(Surgery, Radiotherapy and Chemotherapy of Cancer).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 353-357.

The androgen receptors in the human prostate gland were studied using prostatic tissue obtained at retropubic prostatectomy for benign hyperplasia and four samples of normal prostate tissue removed shortly after death. Cytoplasmic extracts were analyzed for steroid-binding components by sucrose gradient ultracentrifugation or gel-exclusion chromatography, and nuclear extracts were prepared in 0.5 M KCl. For *in vivo* labeling, 50 μCi of [^{3}H]-testosterone was administered iv 15-20 min prior to enucleation of the prostatic adenoma. Both nuclear and cytoplasmic androgen receptors were identified in the prostatic tissue, both forms of receptors demonstrating a high affinity but low capacity for 5α-dihydrotestosterone; this binding was highly steroid-specific. The androgen receptors were also tissue-specific and could not be identified in serum or muscle. The cytoplasmic and nuclear forms of receptors differed in physicochemical properties, a conspicuous feature of the cytoplasmic, but not the nuclear, extracts being the presence of nonspecific binding proteins; this binding was of low affinity but high capacity. Positive identification of androgen receptors may be reflected in the analytical procedure adopted; in general, gradients are more reliable for labile receptors than charcoal procedures. Androgen receptors may be a characteristic and invariant feature of the human prostate gland. Although surgery will remain the treatment of choice for benign prostatic hyperplasia in the near future, ablation of the androgen-binding process in malignant carcinoma may provide an improved form of treatment as compared with classical estrogen therapy.

3101 SPECIFIC CHROMOSOME CHANGES IN MALIGNANCY: STUDIES IN RAT SARCOMAS INDUCED BY TWO POLYCYCLIC HYDROCARBONS. (Eng.) Levan, G. (Inst. of Genetics, Univ. of Lund, S-22362, Sweden); Levan, A. *Hereditas* 79(2):161-198; 1975.

Karyotypes were analyzed and deviations from normality recorded in conventional preparations of ten rat sarcomas induced by 20-methylcholanthrene (MC) and 13 induced by 3,4-benzpyrene (BP). Whenever possible these observations were supplemented with banding analyses in direct preparations and early cultures. About 1,000 complete karyotypes were analyzed mostly by means of camera lucida drawings.

he variation both of the normal chromosomes and of he markers was nonrandom. Of the normal rat chrosomes only a few specific ones participated regularly in the formation of markers, and structurally dentical or similar markers were demonstrated reeatedly in different sarcomas, often the same mark- r in both MC and BP inductions. This is compatible ith recent observations in human malignancies. The ariability of several parameters (chromosome numers, karyotypic multiformity, incidence of markers nd double minutes) was generally more pronounced in he BP- than in the MC-induced sarcomas, and both roups showed more variable conditions than the sarmas induced by 7,12-dimethylbenz(α)anthracene MBA). Tentatively, this fact was associated with e differences in oncogenic capacity among the ree compunds: DMBA>MC>BP. It is suggested, along e lines of the mutation theory, that a less potent cogen launches a less precise attack on the sigficant gene sites, and consequently more extreme romosome changes will accompany the malignant ansformation.

02 MAMMALIAN CELL TRANSFORMATION AND CELL-MEDIATED MUTAGENESIS BY CARCINOGENIC POLYCLIC HYDROCARBONS. (Eng.) Huberman, E. (Dep. net., Weizmann Inst. Sci., Rehovot, Israel) *Mutat. s.* 29(2):285-291; 1975.

rrelations between mutagenicity and carcinogenity were studied *in vitro* mammalian cell culture stems. In one system, mutagenesis was measured the production of azaguanine resistance in male inese hamster V79 cells. The cells were grown in gle's medium with a 4-fold concentration of amino ids and vitamins and 10% fetal calf serum. Mutanicity was measured by plating 2 x 10^4 cells/dish; ter 16 hr incubation the cultures were treated for ree hours with various concentrations of the test mpounds. The medium was replaced by fresh medium thout the test compounds, and the cells were incuted for 48 hr. The dishes were refed every two ys with medium containing 30 μg/ml of 8-azaguanine 0.5% dimethyl sulfoxide. Ten to 14 days after the itial addition of 8-azaguanine, the resistant colies were fixed, stained, and their number was dermined. The mutation frequency was calculated per ^{5} survivors. Using this method, reactive chemical rcinogens such as *N*-methyl-*N'*-nitro-*N*-nitrosoguanine, *N*-acetoxy-*N*-2-fluorenylacetamide and K-region oxides of polycyclic hydrocarbons were mutagenic the Chinese hamster cells and also transformed lls. The chemically nonreactive carcinogenic polyclic hydrocarbons, which transform rodent cells in lture, were not mutagenic to the V79 cells because ese cells lines do not metabolize polycyclic hyocarbons into mutagenic metabolites. In order to tain better correlations, a cell-mediated mutagenic say with carcinogenic hydrocarbons was developed which Chinese hamster cells, which are susceptie for mutagenesis, were cocultivated with lethally radiated rodent cells that can metabolize these mpounds. Using this cell-mediated assay, mutanesis was obtained with 7,12-dimethylbenz(*a*)anthrane, benzo(*a*)pyrene, 3-methylcholanthrene, and 7-thyl-benz(*a*)-anthracene. The most potent carcino-n, 7,12-dimethylbenz(*a*)anthracene, gave the highest frequency of mutations. The polycyclic hydrocarbons, pyrene and benz(*a*)anthracene, which are not carcinogenic, were also not mutagenic. This assay demonstrates a relationship between the carcinogenicity of polycyclic hydrocarbons and their mutagenicity in mammalian cells, without having to isolate their reactive metabolic intermediates.

3103 THE USE OF THE FLUOROCHROME BIS-BENZIMIDAZOL DERIVATIVE (HOECHST 33258) IN THE STUDY OF SPONTANEOUS AND INDUCED CHROMOSOME ABERRATIONS. (Eng.) Raposa, T. (Semmelweis Univ. Medical Sch., 1430 Budapest 81. POB. 21. Hungary); Natarajan, A. T. *Cytobiologie Z. Exp. Zellforsch.* 11(2):230-239; 1975.

The value of a new fluorochrome bis-benzimidazole derivative in the identification of chromosomal rearrangements in mammalian chromosomes was investigated. Human chromosome preparations were made from phytohemagglutinin-stimulated lymphocytes or fibroblasts, and normal mouse chromosome preparations were made from cultures derived from 12-14-day-old embryos. Chromosome aberrations were induced *in vivo* by treating tumor-bearing mice with mitomycin C (4 μg/ml ascites fluid), and aberrations were produced in normal human peripheral blood chromosomes by *in vitro* treatment with mitomycin C (0.6 μg/ml). The preparations were stained with fluorochrome at 0.1 μg/ml for ten minutes at 37 C; in some cases, the cells were pretreated with DNase (100 μg/ml) for five minutes at 37 C. With the normal human chromosomes, the fluorochrome produced a distinct banding pattern not quite similar to Q-banding. A pattern very similar to Q-banding was also produced with the mouse chromosomes, although, again, there were some differences. With the fluorochrome, the constitutive heterochromatin regions showed bright fluorescence, while the euchromatic regions exhibited a distinct banding pattern, allowing an easy and accurate evaluation. Mild DNase treatment increased the differential affinity of the fluorochrome for the eu- and heterochromatic regions. Mitomycin C-induced aberrations in both human and mouse chromosomes were therefore easily studied. In addition, identification of the Ph' chromosome and the association translocation in chromosome 9 was easy. The value of the fluorochrome in studying the distribution of constitutive heterochromatin regions in mouse tumors was also demonstrated. The new fluorochrome provides a valuable new banding technique. The mechanism of binding of the fluorochrome is unclear.

3104 A RAPID AND SENSITIVE LIQUID CHROMATOGRAPHIC ASSAY FOR EPOXIDE HYDRASE. (Eng.) Nesnow, S. (McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, Wis. 53706); Heidelberger, C. *Anal. Biochem.* 67(2):525-530; 1975.

A rapid method for the assay of epoxide hydrase activity is described. 3-Methylcholanthrene-11,12-oxide is the substrate. High-speed liquid chromatography is used to separate and quantitate *trans*-11,12-dihydro-11,12-dihydroxy-3-methylcholanthrene (product) formation. The product can be determined

at picomole levels. Epoxide hydrase was determined in lower homogenate and microsomes of rats pretreated with 3-methylcholanthrene or phenobarbital. The enzyme levels obtained were comparable to those obtained with the styrene oxide method. An assay requires 35 min with this new method.

3105 RELATIONSHIP OF TUMOR IMMUNOGENICITY TO CONCENTRATION OF THE ONCOGEN. (Eng.) Prehn, R. T. (Inst. for Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, Pa. 19111). *J. Natl. Cancer Inst.* 55(1):189-190; 1975.

Studies were conducted to determine if the immunogenicity of 3-methylcholanthrene (MCA)-induced tumors is related to the concentration of the chemical. Tumors were induced sc in (BALB/c x DBA/2)F_1 female mice by various concentrations of MCA in paraffin pellets. There was an inverse relationship between MCA concentration and tumor latency (interval between MCA implantation and detection of gross tumor). The tumors were transplanted into syngeneic recipients, and material from this first transplant generation was used to immunize a series of syngeneic mice; any resulting growth was excised. Nonimmunized mice were controls. Immunized and control mice were irradiated and given an sc inoculation of a near-threshold number of tumor cells (usually 10^5). Tumor growth from that inoculation was measured weekly in both groups and the antigenicity ratio (mean tumor size in controls/mean tumor size in immunized mice) was calculated. In a series of tumors with similar latencies, the only ones with high antigenicity ratios were those resulting from the high MCA concentration (5%). The results suggest that tumors induced by low levels of oncogen may be good models of spontaneous neoplasia. The data strengthen the hypothesis that "spontaneous" tumors may actually result from low levels of oncogen, and indicate that neoplastic transformation and the development of immunogenicity are, at least in chemically induced tumors, independent changes that may be produced in the same cell when the concentration of oncogen is sufficient.

3106 EFFECT OF 3-METHYLCHOLANTHRENE (NSC-21970) ON HUMAN PROSTATE IN ORGAN CULTURE. (Eng.) Noyes, W. F. (Dept. Biological Resources, Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14203). *Cancer Chemother. Rep. (Part 1)* 59(1):67-71; 1975.

Long-term organ culture of normal human prostatic tissue with demonstration of functional and morphologic maintenance of the glandular epithelium is described. The tissues were obtained from 50- to 70-yr-old patients undergoing cystectomy. They were maintained in McCoy's 5a plus 20% fetal bovine serum and antibiotics, and were maintained as rocker cultures; the rocking motion provided a thin nutrient film and allowed adequate gas exchange (95% O_2, 5% CO_2, pH 7.2). 3-Methylcholanthrene (4 μg/ml) in the culture fluid induced morphologic changes that were not observed in untreated cultures. The changes observed after exposure to the carcinogen for 15-30 days included hyperplasia and anaplasia of the glandular epithelial cells with large variation in nuclear size and shape. These changes are suggestive of a neoplastic potential.

3107 EARLY MORPHOLOGIC ALTERATIONS IN MOUSE SKIN AFTER TOPICAL APPLICATION OF 3-METHYLCHOLANTHRENE AND ITS METABOLITES. (Eng.) Burki, K. (Inst. Pathol., Univ. Berne, Switzerland); Bresnick, E. *J. Natl. Cancer Inst.* 55(1):171-176; 1975.

The early morphologic changes after topical administration of 1.5 or 3 μM of 3-methylcholanthrene (MCA) or its metabolites on BALB/cKi mice were studied. Five days after treatment with MCA, interfollicular epidermis (IFE) cells were increased 340% in height, 256% in area, and 272 in mitoses/unit length. A 2 to 3-fold increase in thickness and number of cell layers was noted. These changes were absent after application of microsomal metabolites or of the "K-region" oxide of MCA. Other MCA metabolites also failed to induce notable inflammation, epidermal hyperplasia, and/or hypertrophy. Several MCA derivatives, however, caused a thinning of IFE paralleled by an increase in the relative number of pyknotic nuclei and a decrease in the total number of epithelial cells. Pretreatment of the skin with α-naphthoflavone potentiated the hyperplastic effects of MCA. The findings indicate that important events in the promotion phase of MCA-mediated skin carcinogenesis might be associated with the parent compound rather than with one of its metabolites.

3108 INCREASED URINARY EXCRETION OF LABELLED DEOXYRIBONUCLEOSIDES IN RATS WITH STABLE PRE-LABELLED DNA TREATED WITH METHYL METHANESULPHONATE OR NITROGEN MUSTARD. (Eng.) Chu, B. C. F. (Chester Beatty Res. Inst., London SW3 6JB England); Lawley P. D. *Chem. Biol. Interact.* 10(6):407-412; 1975.

After the DNA of newborn female CB hooded rats had been labeled by repeated sc injections of [^{14}C]-orotate (totaling 36 μCi) during the first three weeks of life, approximately 1,000,000 dpm were found in the DNA of the liver, lungs, kidneys, gut, brain, heart and spleen of eight-week-old rats. Methyl methanesulfonate (80 mg/kg) and di-(2-chloroethyl)methylamine (5 mg/kg) injection increased the amount of ^{14}C-labeled DNA pyrimidine nucleosides excreted in the urine to 5000 dpm from 350 dpm before injection. The effect on RNA products was much less marked. It is possible that excretion of DNA products may be useful in monitoring the extent of DNA damage in patients undergoing various forms of alkylating agent therapy.

3109 STRUCTURE-ACTIVITY CONSIDERATIONS OF ALKYLATING AGENTS AS MUTAGENS. (Eng.) Bedford, C. T. (Shell Res. Ltd., Kent, England). *Mutat. Res.* 29(2):195-196; 1975.

The relative alkylating and phosphorylating reacti-

ties of organophosphates were studied by comparing eir chemical reactivities towards 4-(*p*-nitroben-l)pyridine (NBP) and hydroxide ion (OH^-). I-Chlo-ethenyl dimethyl phosphate is one tenth as reac-ve as methyl methanesulfonate (MMS). If it were *ly* an alkylating agent its reactivity towards OH^- uld also be one tenth that of MMS. In fact, re-tivity towards OH^- is 2750 x larger than this. e phosphorylating reactivity of I-chloroethenyl thyl *N,N*-diethylphosphoramidate decreased by a ctor of 10^{-4}, but its alkylating reactivity only a factor of about 30. NBP was also used to mea-re the relative alkylating reactivities of methyl d ethyl iodide, dimethyl and diethyl sulfates, thyl and ethyl methanesulfonates, and trimethyl d triethyl phosphates. It was found that the lides are intermediate in reactivity between the fates and the sulfonates, and that methyl com-unds are 18 to 40-fold more reactive than ethyl npounds. A close parallel with these chemical ctivities was noted when these same four pairs of npounds were tested for mutagenic activity in st (gene conversion frequency in *Saccharomyces evisiae* at the Ade_2 (adenine) locus).

0 METHYLATION OF DNA IN VARIOUS ORGANS OF C57Bl MICE BY A CARCINOGENIC DOSE OF *N*-HYL-*N*-NITROSOUREA AND STABILITY OF SOME METHYL-ON PRODUCTS UP TO 18 HOURS. (Eng.) Frei, J. V. ester Beatty Res. Inst., London SW3 6JB England); ley, P. D. *Chem. Biol. Interact.* 10(6):413-427; 5.

ale C57Bl mice (aged 6-8 wk) were injected ip n *N*-methyl-*N*-nitrosourea (MNUA ^{14}C or ^{3}H-*methyl*-eled) in saline (80 mg/kg) and DNA was isolated n bone marrow, small bowel, kidneys, liver, lungs, een, and thymus at various times thereafter up to nr. Methylation of DNA was found in all organs nined, and by analyses using column or paper matography of DNA hydrolysates, the extent of ylation of DNA purines was determined. Methyl-l guanine residues (at N-3, N-7 and O-6 positions) stable in DNA up to 18 hr, but methylated ade-s (at N-3 or N-7) were removed from DNA of all ns examined; the overall half-life of methylade-s was about 3 hr, but removal appeared to occur biphasic manner, with a proportion of methyl-ine remaining relatively stable. This relative ility was somewhat more marked in bone marrow in other organs. The pattern of DNA methylation NUA is compared with that previously observed methyl methanesulfonate (MMS); unlike MNUA, MMS not induce thymomas in mice despite its ability ethylate tissue DNA to the same extent as the er compound. Differences in the mechanisms of on of the two methylating agents are outlined.

ASSAYS FOR PHOSPHOTRIESTER FORMATION IN THE REACTION OF BACTERIOPHAGE R17 WITH A P OF ALKYLATING AGENTS. (Eng.) Shooter, K. V. al Cancer Hosp., London SW3 6JB Great Britain). . *Biol. Interact.* 11(6):575-588; 1975.

interaction of bacteriophage R17 with eight com-ds was studied, comparing the contribution of degradation of RNA to the total toxicity. Breaks in the RNA chain result from the hydrolysis of phosphotriesters, and were thus used as a measure of the extent of *O*-alkylation and of the S_N1-type mechanism of the reaction. In experiments with methyl methanesulphonate, no evidence of degradation was observed at up to 19 times the mean lethal dose (620 methylations/RNA molecule). Breaks in the RNA chain accounted for 1 in 10 of the lethal lesions with β-hydroxyethyl methanesulphonate, 1 in 60 with bis-(2-chloromethyl)methylamine (nitrogen mustard, HN2), less than 1 in 125 with 2,2-dichlorvinyl dimethyl phosphate (dichlorvos, DDVP), and 1 in 200 with propylene oxide. The hydrolysis rate of bis-(2-chloroethyl)ether was too slow for any reaction to be detected. In reactions with the carcinogen bis-(2-chloromethyl)ether, the toxicity observed could be accounted for by the formaldehyde produced on hydrolysis. Cross-linking of the bacteriophage components by formaldehyde reduced the survival range over which the physical state of the RNA could be studied. No evidence of RNA degradation was observed. Reaction of the formaldehyde led to a progressive loss of biological activity over 24 hr, a loss which was partially reversed by dialysis. The results suggest that the existence of *O*-alkylation as visualized by degradation following phosphotriester formation correlates with the known mutagenicity of some compounds.

3112 NEURO-ONCOGENIC ALKYLATING AGENTS: PERINATAL CARCINOGENESIS VERSUS APPLICATION IN ADULT ANIMALS. (Eng.) Kleihues, P. (Max-Planck-Institut für Hirnforschung, Abteilung Allgemeine Neurologie, 5 Köln-Merheim, West Germany); Margison, G. P. *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 146-149.

The relative amounts of methylguanine found in cerebral DNA hydrolysates of animals injected with methylnitrosourea or methyl methanesulphonate were measured chromatographically. Alkylguanine is an indicator of alterations in the DNA molecule because: (1) it is capable of miscoding (2) potent carcinogenic agents produce the base to a greater extent than weaker carcinogenic agents. Methyl methanesulfonate is an example of the group of potent carcinogens which alkylate DNA via a free alkyl carbonium ion released in chemical or enzymatic degradation of the compound. The agent was injected (50 mg/kg, sc) into newborn BD-IX rats, killed two hours later in order to measure the DNA cerebral hydrolysates. Methylnitrosourea (80 mg/kg, iv) was administered to adult BD-IX rats, killed six hours later. A weaker carcinogen, methylnitrosourea is an example of agents which react with DNA by direct transfer of an alkyl group. The relative amounts of methylguanine produced by equimolar doses of these agents differed by a factor of about 20 with methyl methanesulfonate injection resulting in the higher amount. Susceptibility to neurooncogenic agents is maximal in the fetal and newborn rat and decreased to the adult level about one month post-natally. The difference in methylguanidine

levels in the DNA cerebral hydrolysates may be attributable to the ages of the animals as well as the carcinogenic action of the compounds.

3113 AMELOBLASTIC ODONTOMA IN RATS INDUCED BY N-BUTYLNITROSOUREA. (Eng.) Wang, H.-H. (Kagoshima Univ. Sch. Medicine, Usuki-cho, Kagoshima 890, Japan); Terashi, S. I.; Fukunishi, R. *Gann* 66(3):319-321; 1975.

Four cases of ameloblastic odontomas were found in 68 Long-Evans rats treated with po administration of 300 mg/kg N-butylnitrosourea four times biweekly. The tumor was found as an expansive enlargement over the mandible and was roentgen-opaque. It was histologically characterized by various elements such as odontogenic epithelium, stellated reticulum tissue, enamel, and/or dentine, and was classified as ameloblastic odontoma. It is concluded that, although the present incidence is not high enough, N-butylnitrosourea and the Long-Evans strain may be a good combination for the induction of odontogenic tumors in rats.

3114 MACROPHAGES IN BRAIN TUMOURS INDUCED TRANSPLACENTALLY BY N-ETHYL-N-NITROSOUREA IN RATS: AN ELECTRON-MICROSCOPE STUDY. (Eng.) Lantos, P. L. (Middlesex Hosp. Medical Sch., London, England). *J. Pathol.* 116(2):107-115; 1975.

The fine structure of macrophages was studied in experimental brain tumors induced transplacentally in BD-IX rats by a single iv injection of 30 mg of N-ethyl-N-nitrosourea/kg on the 15th day of gestation. The tumors, depending on their localization and size, caused various lesions in the brain, namely axonal degeneration, loss of myelin, edema, hemorrhage and cell necrosis. The tumors and the resulting alterations elicited a strong reaction by macrophages; activation of microglial cells *in situ* and infiltration of the brain by leucocytes, chiefly monocytes. Since both microglial cells and monocytes underwent morphological changes, it was difficult, or impossible, to establish the origin of these reacting cells. In a few cases, however, microglial cells and monocytes could be distinguished, indicating that microglial cells were still being activated and leucocytes were still entering the brain. The number of lysosomes and cytoplasmic inclusions was thought to indicate activation, phagocytosis and repletion. Activation was characterized by an increase of lysosomes and by frequent cell divisions. Phagocytic activity was accomplished by the appearance of inclusions which varied in different lesions: protein-like material in edema, remnants of erythrocytes in hemorrhages and myelinlamellae with lipid droplets in demyelination. These various inclusions were frequently present in the same cell, since the different lesions not uncommonly occurred at the same time. In the stage of repletion macrophages contained mainly lipid droplets and unidentifiable debris in their abundant cytoplasm and thus corresponded to the compound granular corpuscles.

3115 PROTEIN CHAIN INITIATION *IN VITRO* BY LIVER CELL COMPONENTS FROM DMNA-TREATED RATS. (Eng.) Nygard, O. (Dept. Cell Physiology, Wenner-Gren Inst., S-113 45 Stockholm, Sweden); Hultin, T. *Chem. Biol. Interact.* 11(6):589-598; 1975.

The mechanism of inhibition of protein synthesis in rat liver after dimethylnitrosamine (DMNA) administration was studied at the level of peptide-chain initiation by use of initiation-dependent amino acid incorporating systems. Ribosomal monomers, poly(A)-containing RNA from monosomes and polysomes, and crude initiation factors from microsomes were prepared two hours after a single ip injection of DMNA (75 mg/kg), and their activities in the production of new protein chains were determined under conditions of nearly linear response. Monosomes and crude initiation factors from DMNA-treated rats were at least as active as those from controls. Preparations of poly(A)-containing RNA had a consistently higher template activity when prepared from polysomes instead of monosomes. However, in neither case was there any loss of activity due to the DMNA treatment. The poly(A)-containing RNA was methylated by DMNA to about the same extent as the 18S and 28S ribosomal RNA. The methylation was consistently somewhat higher in the RNA preparations from monosomes than in those from polysomes. The results suggest that the inhibiting effect of DMNA on liver protein synthesis is indirect and possibly mediated through regulatory functions.

3116 A RAPID METHOD FOR THE DETERMINATION OF SUB-PART PER BILLION AMOUNTS OF N-NITROSO COMPOUNDS IN FOODSTUFFS. (Eng.) Fine, D. H. (Thermo Electron Corporation, 85 First Ave., Waltham, Mass. 02154); Rounbehler, D. P.; Oettinger, P. E. *Anal. Chim. Acta* 78(2):383-389; 1975.

A new analytical clean-up technique, designed specifically for the analysis of N-nitroso compounds in food samples with a thermal energy analyzer and a gas chromatograph, is described. Only two steps are required: (a) vacuum distillation of about 20 g food sample, 4 ml 0.1 M sodium hydroxide, and 20 ml crude mineral oil; and (b) extraction with dichloromethane (three times with 5 ml). The extracts can then be analyzed by gas chromatography and a thermal energy analyzer; the sensitivity for N-nitroso compounds in foodstuffs is at the 5 μg kg^{-1} level, but if a dichloromethane extract is concentrated on a Kuderna Danish evaporator, a 100-fold increase is attainable. The method can be used for any foodstuff or biological material, and the quantitation of any N-nitroso compounds amenable to gas chromatography is possible.

3117 TUMORIGENESIS BY OXYGENATED NITROSOPIPERIDINES IN RATS. (Eng.) Lijinsky, W. (Oak Ridge Natl. Lab., Oak Ridge, Tenn. 37830); Taylor, H. W. *J. Natl. Cancer Inst.* 55(3):705-708; 1975.

The effects of three oxygenated N-nitrosopiperidines (nitroso-3-piperinol, nitroso-4-piperidinol, and nitroso-4-piperidone) given at equivalent molar

ses to rats were investigated. Each compound was ven in drinking water to a group of 8- to 10-wk- d male (15) and female (15) Sprague-Dawley rats. trosopiperidine was given for 44 wk, while the her three compounds were given for 36 wk. All bstances were potent carcinogens; 100% of the rats veloped tumors in all treatment groups. Nitroso- piperidinol resembled nitrosopiperidine in inducing high incidence of tumors of the nasal cavity and per alimentary tract and a few liver tumors. Ni- oso-4-piperidinol and nitroso-4-piperidone caused high incidence of tumors of the nasal cavity, but ry few tumors of the upper alimentary tract. Af- r treatment with the 4-substituted compounds, a gh incidence of liver tumors was observed in fe- les, but not in males; this may thus demonstrate e influence of sex hormones on the induction and velopment of tumors in liver cells of rats.

18 DAMAGE TO MAMMALIAN CELL DNA BY NITRO- FURANS. (Eng.) Olive, P. L. (Dep. Bio- em., McMaster Univ., Hamilton, Canada); McCalla, R. *Cancer Res.* 35(3):781-784; 1975.

e effects of nitrofuran derivatives on DNA of mam- lian L929, KB, and BHK-21 cells *in vitro* and Ehr- ch ascites cells *in vivo* was studied under varying ates of oxygenation. Maximum rates of nitrofura- ne reduction by intact mammalian cells and by mouse ver homogenates (9,000 x *g* supernatant) occurred der anaerobic conditions, although considerable re- ction did occur with gas mixtures of 5% O_2. Nitro- azone treatment (250 μM, 90 min) resulted in sin- e strand DNA breaks (as determined by alkaline su- se gradients) under anaerobic conditions in the ee mammalian cell lines, and the effect was dose- endent. No such damage occurred under aerobic ditions, even at 500 μM nitrofurazone. In Ehrlich cites cells from mice treated with nitrofurazone mg, i.p.), the DNA damage was maximum at 30 min er treatment, and by 100 min the sucrose gradient approaching normal. The breaks in the DNA of the tured lines was not reversible up to four hr af- treatment. The authors conclude that nitrofu- s might be of use in increasing radiosensitivity the radiotherapy of those solid tumors which con- n poorly oxygenated cells.

9 HISTOLOGICAL CHANGES OF TERMINAL BRON- CHIOLES IN RATS DURING THE EXPOSURE TO ROGEN DIOXIDE. (Eng.) Rejthar, L. (Inst. Occu- . Dis. of Univ. J. E. Purkyne, Pekarska 53, 65 Brno, Czechoslovakia); Rejthar, A. *Exp. Pathol. na)* 10(5/6):245-250; 1975.

course of histological changes in the epithelium the terminal bronchioles during the long-term tinuous exposure of rats to low concentrations of (5 ppm wt/wt) in air was studied. At intervals 3, 4, 7, 9, and 11 wk from the beginning of ex- ure, three experimental and 1-2 control animals e killed, and their lungs were examined histo- ically. The first changes were the loss of cilia cell differentiation. These changes were fol- ed by epithelial hyperplasia, leading to con- cuous narrowing of the lumen of bronchioles. The hyperplastic phase was followed by a phase of reparation, leading to the development of non- ciliated epithelium without observable clear cells, and areas of uniform multi-layered epithelium. After 11 wk, new changes analogous to those found at the beginning of the experiment were observed.

3120 INHIBITORS OF POLYAMINE BIOSYNTHESIS. 3. (±)-5-AMINO-2-HYDRAZINO-2-METHYLPENTANOIC ACID, AN INHIBITOR OF ORNITHINE DECARBOXYLASE. (Eng.) Abdel-Monem, M. M. (Coll. Pharmacy, Univ. Minnesota, Minneapolis, Minn. 55455); Newton, N. E.; Weeks, C. E. *J. Med. Chem.* 18(9):945-948; 1975.

(±)-5-Amino-2-hydrazino-2-methylpentanoic acid (α-hydrazino-α-methyl-(±)-ornithine) was synthesized and evaluated as an inhibitor of ornithine decarboxylase *in vitro* and in transforming lymphocytes. The title compound was obtained from 1-phthalimidopentan-4-one by treatment with hydrazine and KCN followed by acid hydrolysis. The title compound was found *in vitro* to be a potent competitive inhibitor of ornithine decarboxylase obtained from the prostate glands of rats. It was approximately 10 times more potent than alpha-methyl-(±)-ornithine and equipotent to alpha-hydrazino-L-ornithine *in vitro*. This inhibition was abolished at high concentrations of pyridoxal phosphate. The title compound also blocked the increase in putrescine levels normally observed in bovine lymphocytes transformed by conconavalin A.

3121 CYTOLOGICAL STUDIES ON ONION ROOT-TIP CELLS TREATED WITH WATER-SOLUBLE EXTRACT OF TOBACCO SMOKE CONDENSATE FROM COMMERCIAL CIGARETTES. (Eng.) Sabharwal, P. S. (T. H. Morgan Sch. Biological Sciences, Univ. Kentucky, Lexington, Ky.); Gulati, D. K.; Bhalla, P. R. *Mutat. Res.* 31(4): 217-224; 1975.

The effect of water-soluble extract of tobacco smoke condensate (TSC) from two commercially available cigarettes with different types of filters was studied on the cytology of root-tip cells of onion *(Allium cepa)*. One of the cigarettes had a 2-cm cellulose acetate filter, and the other had a filter comprised of 1 cm of cellulose acetate and 1 cm of activated charcoal. A total of 840 cigarettes were smoked on a smoking machine, and the smoke was collected in a flask containing 100 ml of water cooled to 2 C. The flask was rinsed with water to give a final concentration of 50 mg/ml of nonvolatile residue. This TSC was subsequently diluted with distilled water to make 0.01, 0.025, 0.05, 0.1, and 0.25% test concentrations. The treatment was given by placing the onion bulbs with roots dipping in small vials containing 15 ml of TSC solution for 24 hr. TSC induced mitotic abnormalities; with increasing concentrations (0.01% to 0.1%) of TSC from cigarettes with filters and defiltered, percent mitotic abnormalities increased. These abnormalities included scattering, stickiness, lagging, condensation, and breaking of chromosomes during metaphase. Bridging and lagging of chromosomes were observed during anaphase. To investigate whether these two commercial filters could retain cigarette smoke component(s) responsible for mitotic irregu-

larities, the cigarettes were defiltered, and TSC was prepared and tested on the young roots of onion. The cytological effect of TSC from defiltered cigarettes was not significantly different from the effect of TSC from cigarettes with filters. Thus, the filters utilized in these cigarettes do not retain compound(s) responsible for mitotic irregularities in the root-tip cells of onion.

3122 INHALATION EXPERIMENTS WITH ^{14}C-LABELLED CIGARETTE SMOKE. I. DETERMINATION OF THE EFFECTIVENESS OF TWO DIFFERENT SMOKING SYSTEMS WITH LABELLED CIGARETTES. (Eng.) Reznik, G. (Medizinische Hochschule Hannover, 3000 Hannover-Kleefeld, Karl-Wiechert-Allee 9, West Germany); Kmoch, N.; Mohr, U. *Toxicology* 4(3):363-371; 1975.

Two different types of smoking systems (type RM 20/68 and type Hamburg II) were tested by exposing Syrian golden hamsters to the smoke from 60 mm cigarettes labeled with [^{14}C]dotriacontane-16,17 (DOT, 55 mCi/M). Two experiments were performed using the first type of smoking system, where individual animals were exposed to the smoke from four cigarettes (12 μCi [^{14}C]DOT/cigarette in the first experiment, and 12.8 μCi [^{14}C]DOT/cigarette in the second experiment). The third experiment utilizing the type Hamburg II system involved ten hamsters exposed simultaneously to smoke from 30 cigarettes (10.6 μCi [^{14}C]DOT/cigarette). In each experiment, the radioactivity of mainstream and sidestream total particulate matter (TPM), and of butts and ash was determined. In the system involving individual animal exposure, more than 4% of the radioactivity was found in the animals, whereas with group exposure only 1% of the total radioactivity passed into the animals. Therefore, the type RM 20/68 smoking system seemed to be preferable for obtaining high quantities of mainstream TPM for inhalation studies on induction of a pulmonary carcinoma.

3123 CLONAL ISOLATION OF EPITHELIAL CELLS FROM MOUSE LUNG ADENOMA. (Eng.) Stoner, G. D. (Sch. of Medicine, Univ. of California at San Diego, La Jolla, Calif. 92037); Kikkawa, Y.; Kniazeff, A. J.; Miyai, K.; Wagner, R. M. *Cancer Res.* 35(8):2177-2185; 1975.

The clonal isolation and characterization of an epithelial cell line derived from an A/He mouse lung adenoma (LA-4) induced by a 20-mg, ip injection of urethan are described. The clone LA-4 cells were characterized with respect to morphology, karyotype, growth, tumorigenicity, mycoplasma contamination, and response to an 8-mo treatment of hydrocortisone (HC, 1.4 x 10^{-5} M). The LA-4 cells and the tumors produced in athymic, nude mice by HC-treated LA-4 cells were examined microscopically. The parental adenoma cells appeared to be composed of a mixture of epithelial and fibroblastic cells; lamellar inclusions were observed in the epithelial-like, but not the fibroblast-like, cells. The clonal LA-4 cells were also epithelial in nature and contained inclusion bodies with a dense, concentric lamellar structure. The LA-4 cells, like their parental precursors, were aneuploid, and all chromosomes were telocentric with no apparent translocations. Only after about 45 clonal transfers did the cells show some tendency toward loss of contact inhibition, however, and they grew more slowly than most tumor cells in culture. LA-4 cells did not produce tumors after sc inoculation into ALS-treated A/He mice or athymic, nude mice. HC stimulated the growth of LA-4 cells and led to the eventual acquisition of neoplastic potential. Epithelial tumors were produced by HC-treated LA-4 cells more readily in athymic, nude mice than in ALS-treated A/He mice. HC treatment did not increase the number of lamellar bodies per cell, and lamellar bodies were not observed in tumors produced by the sc inoculation of parental adenoma cells or HC-treated AL-4 cells. C-type RNA virus particles were observed in all tumors. It is suggested that HC accelerated, rather than induced, transformation in the LA-4 cells.

3124 THE BIOLOGICAL FATE IN RATS OF VINYL CHLORIDE IN RELATION TO ITS ONCOGENICITY. (Eng.) Green, T. (Central Toxicology Lab., Alderley Park, Cheshire, SK10 4TJ Great Britain); Hathway, D. E. *Chem. Biol. Interact.* 11(6):545-562; 1975.

The biological fate of [^{14}C]vinyl chloride after po, iv or ip administration to male Wistar rats was investigated. The main eliminative route was found to be pulmonary; both unchanged vinyl chloride and related CO_2 were excreted by the lungs, and other ^{14}C-labeled metabolites were excreted by the kidneys. After intragastric administration, pulmonary output of unchanged vinyl chloride was proportional to the logarithm of reciprocal dose. Excretion patterns after iv and ip injections were predictable from the characteristics of excretion following po administration. Pulmonary excretion of unchanged vinyl chloride after po dosing was complete within 3-4 hr, but pulmonary elimination of CO_2 and renal excretion of metabolites occupied three days. In comparison, 99% of a small iv dose (250 μg/kg) was excreted unchanged with one hour of injection; 80% within two minutes. The rate of elimination of single po doses of [^{14}C]vinyl chloride was uninfluenced by up to 60 days' chronic dosing with the unlabeled substance. The distribution volume of vinyl chloride as displayed by whole-animal autoradiography agreed with deductions from excretion data. Small localization of ^{14}C in the para-auricular region of appropriate sections occurred in sectioned tubules, belonging possibly to the Zymbal glands. Biotransformation of vinyl chloride into *S*-(2-chloroethyl) cysteine and *N*-acetyl-*S*-(2-chloroethyl) cystein occurred through addition of cysteine, and bio-transformation into: (1) chloroacetic acid, thiodiglycollic acid and glutamic acid, and (2) into formaldehyde (methionine, serine), CO_2 and urea was explicable in terms of an associative reaction with molecular O_2 involving a singlet oxygen bonded transition state in dynamic equilibrium with a cyclic peroxide ground state. There was no evidence for chloroethylene oxide formation. C_2 and C_1 alkylation of intermediary metabolites may be involved in the production of glutamic acid and thiodiglycollic acid from chloroacetic acid. This type of reaction in another

iological situation may lead to transcriptional hanges of the RNA, DNA, or other macromolecular cell onstituents, which would appear to be responsible or vinyl chloride-induced liver neoplasms.

125 MUTAGENICITY OF CHLOROACETALDEHYDE, A POSSIBLE METABOLIC PRODUCT OF 1,2-DICHLOOETHANE (ETHYLENE DICHLORIDE), CHLOROETHANOL (ETHLENE CHLOROHYDRIN), VINYL CHLORIDE AND CYCLOPHOSHAMIDE. (Eng.) McCann, J. (Biochemistry Dept., niv. California, Berkeley, Calif. 94720); Simmon, .; Streitwieser, D.; Ames, B. N. *Proc. Natl. Acad. ci. USA* 72(8):3190-3193; 1975.

rapid, sensitive bacterial test to detect chemical rcinogens as mutants utilizes a special set of stidine mutants of *Salmonella typhimurium* for reersion, and a rat (or human) microsomal system for tabolic conversion of carcinogens to their active rms. The mutagenicity of chloroacetaldehyde was sted in this system because the compound is a posble metabolite in mammals of the large-volume instrial chemicals 1,2-dichloroethane (ethylene diloride; 3.5 billion kg/yr, U.S.) and vinyl chlode (2.5 billion kg/yr, U.S.), and of the antineoastic agent, cyclophosphamide. Chloroacetaldehyde fectively reverted a new *Salmonella* bacterial test- strain (TA100) at all levels tested (1-5 mg). loroacetaldehyde was hundreds of times more effecve in reverting TA100 than was chloroethanol (ethene chlorohydrin), a known metabolic precursor of loroacetaldehyde and a possible metabolite of diloroethane and vinyl chloride; or vinyl chloride, ich is itself mutagenic for TA100. Chloroethanol s activated by rat and human liver homogenates to more highly mutagenic form with reversion properes similar to chloroacetaldehyde. Reversion prorties of cyclophosphamide after *in vitro* metabolic tivation suggests that chloroacetaldehyde is not e active mutagenic form of this antineoplastic ug. The likely involvement of chloroacetaldehyde the metabolism of dichloroethane and chloroethanol licates that the carcinogenicity of these indusal chemicals should be thoroughly examined.

26 EXTENT AND DURATION OF COVALENT BINDING OF CARCINOGEN RESIDUES TO THE NUCLEAR DNA DIFFERENT CELL POPULATIONS IN PRECANCEROUS LIVER ostract]. (Eng.) Goodman, J. I. (Dept. Pharology, Michigan State Univ., East Lansing, Mich. 824). *Proc. Am. Assoc. Cancer Res.* 16:4; 1975.

27 STANDARDIZATION OF A HAMSTER CELL *IN VITRO* CARCINOGENESIS BIOASSAY USING CELLS ORED IN LIQUID NITROGEN [abstract]. (Eng.) Pien- R. J. (NCI Frederick Cancer Res. Center, Fredck, Md. 21701); Poiley, J. A.; Lebherz, W. B., . *Proc. Am. Assoc. Cancer Res.* 16:24; 1975.

8 CHANGES IN NUCLEOTIDE COMPOSITION OF NUCLEAR DNA DURING INDUCTION OF HEPATIC CINOMA IN RATS FED CARCINOGENS [abstract]. g.) Firminger, H. I. (Univ. Maryland Medical ., Baltimore, Md. 21201); Kim, K. M.; Morrison, M. *Proc. Am. Assoc. Cancer Res.* 16:11; 1975.

3129 THE EFFECTS OF SEVERAL CROTON OIL CONSTITUENTS ON DNA REPAIR AND CYCLIC NUCLEOTIDE LEVELS IN CULTURED MAMMALIAN CELLS [abstract]. (Eng.) Yager, J. D. Jr. (McArdle Lab., Univ. Wisconsin, Madison, Wis. 53706); Trosko, J. E.; Butcher, F. R. *Proc. Am. Assoc. Cancer Res.* 16:10; 1975.

3130 9-AMINOACRIDINE MUTAGENESIS OF BACTERIOPHAGE T4 INTRACELLULAR DNA. (Eng.) Altman, S. (Dept. Biology, Yale Univ., New Haven, Conn.); Warner, V. *Mol. Gen. Genet.* 138(4):333-343; 1975.

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3177 ESTIMATING THE MAXIMUM TEST DOSE IN CARCINOGENESIS BIOASSAYS USING COMPUTERIZED DATA HANDLING AND ANALYSIS [abstract]. (Eng.) Gordon, E. (NCI Frederick Cancer Res. Center, Frederick, Md.); Riggs, C.; Bostian, P.; Ulland, B. M.; Callahan, L. *Toxicol. Appl. Pharmacol.* 33(1):164; 1975.

See also:

* (Rev): 3001, 3002, 3003, 3004, 3005, 3006, 3007, 3008, 3033, 3034, 3035, 3037, 3039, 3040, 3041, 3042, 3043, 3044, 3045, 3046, 3047, 3048, 3049
* (Phys): 3101, 3103
* (Viral): 3217, 3229, 3249, 3268, 3270, 3275, 3280
* (Immun): 3299, 3303, 3307, 3309, 3342, 3372
* (Path): 3431, 3432
* (Epid-Biom): 3510, 3517, 3518, 3519, 3520, 3529, 3530

78 DISTRIBUTION AND EXCRETION OF THREE CHEMICAL SPECIES OF ^{239}Pu(IV) IN THE BEAGLE.
Eng.) Stevens, W. (Dept. Anatomy, Univ. Utah, alt Lake City, Utah, 84132); Stover, B. J.; Atherton, D. R.; Bruenger, F. W. *Health Phys.* 28(4):387-94; 1975.

e early retention and distribution of ^{239}Pu in the e beagle were compared following iv administration ^{239}Pu (IV) as the transferrin complex (Pu-Tf), a plutonium complex in citrate buffer (Pu-Cit) pH 3.5, and as a particulate Pu(IV) in colloidal rm (Pu-P). The early distribution and retention Pu(IV) at 14 days after injection Pu-citrate and -transferrin were indistinguishable. There was difference in urinary excretion patterns. Deposion, microdistribution, and retention after adminiration of a suspension of particulate Pu(IV) difred greatly from those seen in dogs injected with ue solutions of plutonium. After injection of -Tf or Pu-Cit, the nuclide was cleared from cirlation at a slow rate. Approximately 30% was posited in the liver, ∿50% in the skeleton and % in other soft tissues. Pu-P left the circulaon at a very fast rate, ∿70% was deposited in the ver, with only 2% in the bone and ∿24% in other ft tissue. Only an insignificant fraction of the jected Pu-P was excreted. In the liver, the miodistribution after injection of Pu-Tf and Pu-Cit s uniform and Pu(IV) was associated first with luble protein and later transferred to subcellur liver particles. After injection of Pu-P the crodistribution was heterogeneous; most of the (IV) was located in reticuloendothelial cells d little was associated with soluble proteins. ter injection of Pu-Cit and Pu-Tf, Pu(IV) was und on bone surfaces, while after injection of -P, the small amount of Pu(IV) present was loted exclusively in macrophages of the bone marrow. ese results clearly demonstrate that the distrition and excretion of ^{239}Pu are directly related its chemical identity at the time it reaches cirlation.

79 THICKNESSES OF THE DEPOSITS OF PLUTONIUM AND RADIUM AT BONE SURFACES IN THE BEAGLE.
ng.) Schlenker, R. A. (Radiological and Environntal Res. Div., Argonne Natl. Lab., Argonne, Ill. 439); Marshall, J. H. *Health Phys.* 29(5):649-654; 75.

asurements of the maximum thicknesses of plutonium-9 and radium-226 deposits at endosteal bone surces in beagle dogs were determined by measuring e energy loss of α-particles emitted from the bone rfaces. For the plutonium-239 measurements, bone s taken from a 2-yr-old beagle dog that had been jected with 0.32 μCi/kg monomeric plutonium-239 in trate solution and sacrificed 90 days later. For e radium-226 measurements, bone was taken from a yr-old dog that had been injected with 0.1 μCi/kg ^{6}RaCl$_2$ and 15 μCi/kg ^{133}BaCl$_2$. The dog was sacrized five hours after injection. Samples of endoeal bone with the smoothest surfaces were chosen r measurement. They were placed in vacuum chamrs, and the energy spectra of alpha particles emitted from the surfaces were measured using silicon surface barrier alpha particle detectors. In autoradiographs of transverse sections of diaphyseal bone, the endosteal surfaces showed intense labeling. In the case of plutonium-239, there was no evidence of burial of the surface deposit by appositional bone growth. The thickness of the initial deposit of plutonium-239 was $\leq$ 0.2 μm; for radium-226, the thickness was $\leq$ 6.5 μm. Equations are presented for dose calculation in which a deposit of infinitesimal thickness is assumed. When using these equations, the error introduced for plutonium dose is small; in the case of radium, the greater thickness of the deposit would result in a somewhat greater error. If plutonium-239 were deposited in uniform concentration to a depth of 0.2 μm, then the rate of escape of α-particle energy from the surface would be 98% of that from a plane surface source of infinitesimal thickness. For radium-226 uniformly deposited to a depth of 5 μm, the energy escape would be 76-81% of that from a surface source of infinitesimal thickness, depending on the assumption made about retention of daughter products.

3180 COMPARATIVE METABOLISM OF RADIONUCLIDES IN MAMMALS—IX. RETENTION OF ^{75}Se IN THE MOUSE, RAT, MONKEY AND DOG. (Eng.) Furchner, J. E. (Los Alamos Scientific Lab., Univ. California, Los Alamos, N.M. 87544); London, J. E.; Wilson, J. S. *Health Phys.* 29(5):641-648; 1975.

Whole-body retention of ^{75}Se-selenite in mice, rats, dogs and monkeys was determined with 4π liquid scintillation counting after oral and iv administration in all species, and after ip injection in mice and rats. Oral administrations in rats and mice were made by gastric intubation, and an additional group of mice were given ^{75}Se in their drinking water. The selenious acid was diluted with 0.01 N HNO immediately before injection. Mice and rats were injected with 0.1 cm^3 and dogs and monkeys with 0.5 cm^3 of solution. The group of 40 mice given ^{75}Se in the drinking water received a daily dose of 65 nCi for up to 112 days. Whole-body activities were measured periodically before and at death, when the following tissues were removed and assayed for ^{75}Se activity: pelt, brain, heart, lung, gut (esophagus to rectum, with contents), spleen, liver and kidney. Blood, fat, mesenteries and urogenital organs were pooled and assayed. The residual carcass was assayed as a unit. More than 90% was absorbed from the gut in all species but monkeys, where much less was absorbed. Retention was described by the sum of three exponentials in all species, whatever the route of administration. Effective half-times of the long components increased with body weight. The kidney was the most important emunctory for ^{75}Se after the first three days in all species and for all routes of administration. Radiation protection guides (indicating the concentration level in water deemed to produce no detectable effects) were estimated to be 1.5 nCi/cm^3, which is half the value given as the radiation protection guide for continuous exposure. Figures given in previously published reports are discussed and compared.

3181 INVESTIGATION OF IMMUNOGLOBULIN (IgG, IgA, IgM) LEVELS IN THE BLOOD SERUM OF URANIUM MINERS AFTER HIGHER AND LOWER EXPOSURE TO IONIZING RADIATION. (Eng.) Andrlíková, J. (Res. Dep. Health Inst. Uranium Ind., Pribram, Czechoslovakia); Wagner, V.; Pálek, V. *Strahlentherapie* 149(2):212-218; 1975.

Serum immunoglobulin (Ig) G, A, and M levels were measured in 35 uranium miners (average age 29.9 yr) in a mining district where an increase in exposure to ionizing radiation occurred after a geological disturbance. Serum samples were obtained before the men starting working in the mine and after 1 and 2 yr of work in the mine. The second sampling followed the geological disturbance, which increased the mean exposure to ^{222}Rn daughters to 7.35 Working Level Months (WLM) for about three months. During the second year of work, the mean exposure was as low as 0.13 WLM. IgG and IgM levels decreased significantly after one year of exposure in the mine environment, while the IgA level changed only slightly. After the second year, the IgG and IgM levels rose significantly; IgG exceeded the initial levels to a degree that indicated the occurrence of a regenerative hypercompensation. The IgA level was decreased at this time. There was no correlation between IgA and IgM and the radiation dose rate and only a slight correlation in the case of the decreased IgG levels. In some miners the reduction in IgG reached hypogammaglobulinemic levels after the first year and was followed by a propensity to respiratory tract infections. It is suggested that radiation may damage Ig-producing lymphoid cells through an indirect mechanism and that regenerative mechanisms are not the same for all three Ig classes. The heterogeneity of Ig responses in the miners is in agreement with the hypothesis that different immunosurveillance mechanisms function in the resistance against the growth of emerging lung tumor cells.

3182 AGE-DEPENDENCE OF THE X-RAY-INDUCED DEFICIENCY IN DNA SYNTHESIS IN HeLa S3 CELLS DURING GENERATION 1. (Eng.) Griffiths, T. D. (Washington Univ. Sch. Medicine, St. Louis, Mo. 63110); Tolmach, L. J. *Radiat. Res.* 63(3):501-520; 1975.

The radiation-induced deficiency in DNA synthesis in Generation 1 was studied as a function of the age of HeLa S3 cells at the time of exposure to 220 kV X-rays in the previous generation (Generation 0). The amount of DNA synthesized was dependent on the stage in the generation cycle at which cells were irradiated. The smallest deficiency (20-35% after a dose of 500 rad) was observed in cells irradiated in early G1 or early G2, while the greatest deficiency (55-70% after 500 rad) was found in cells irradiated at mitosis or at the G1/S transition. The high sensitivity of cells at G1/S was also manifested by a steeper dose-response curve. Cells irradiated in late G2, past the point where their progression was temporarily blocked by X-rays, synthesized a normal amount of DNA in Generation 1, while cells held up in the G2 block exhibited deficient synthesis in the next generation. The extent of the deficiency in early G1 cells could be enhanced by treatment with 1 mM hydroxyurea for several hours immediately following irradiation. It is concluded that the amount of DNA synthesized in generation 1 depends on the stage in the cycle at which generation 0 cells are irradiated; cells irradiated at mitosis or the G1/S transition showing the greatest deficiency in synthesis, and those irradiated in early G1 or late S/early G2, the least.

3183 INDUCTION OF CHROMOSOMAL ABERRATIONS IN HUMAN LYPMHOCYTES BY X RAYS AND FISSION NEUTRONS: DEPENDENCE ON CELL CYCLE STAGE. (Eng.) Carrano, A. V. (Lawrence Livermore Lab. Univ. California, Livermore, Calif. 94550). *Radiat. Res.* 63(3):403-421; 1975.

The induction of chromosomal aberrations after irradiation in the different stages of the cell cycle was studied, and relative biological effectiveness values for specific aberration types as a function of dosage and cell cycle stage were determined. Human lymphocytes were irradiated in culture with several doses of 250 kVp X rays or fission neutrons (0.85 MeV average energy) either in the unstimulated state (G_0) at 17 hr after phytohemagglutinin stimulation (G_1) or at approximately 48 hr after stimulation. In the last case, the cells were labeled with tritiated thymidine prior to irradiation to distinguish S and G_2 cells. All cultures were harvested at two successive intervals between 48 and 58 hr. The relative biological effectiveness for total aberration production was highest in G_2, lowest in S, and intermediate in G_1. The frequencies of neutron-induced chromatid deletions in G_2 cells differed significantly among harvest times and definite trends were observed for other aberrations. Dose-response curves for chromosome type aberrations followed the classical aberration production model; chromatid aberrations exhibited more complex kinetics. The differential cell cycle response to aberration induction varied with radiation, quality, dose, and aberration type. The relative biological effectiveness of fission neutrons for aberration production also varied with aberration type, cell cycle stage, and neutron dose but remained principally between 2 and 6.

3184 DIFFERENTIAL REGENERATION OF INTESTINAL PROLIFERATIVE CELLS AND CRYPTOGENIC CELLS AFTER IRRADIATION. (Eng.) Potten, C. S. (Christie Hosp., Manchester M20 9BX, England); Hendry, J. H. *Int. J. Radiat. Biol.* 27(5):413-424; 1975.

3185 QUANTITATIVE DOSE-RESPONSE OF GROWTH AND DEVELOPMENT IN *ARABIDOPSIS THALIANA* EXPOSED TO CHRONIC GAMMA-RADIATION. (Eng.) Daly, K. (Dept. Biology, California State Univ., Northridge, Calif. 91324); Thompson, K. H. *Int. J. Radiat. Biol.* 28(1):61-66; 1975.

3186 CONSEQUENCES OF THYROID RADIATION IN CHILDREN. (Eng.) Braverman, L. E. (St. Elizabeth's Hosp., Boston, Mass.). *N. Engl. J. Med.* 292(4):204-205; 1975.

187 EXPERIMENTAL MANIPULATION OF PRELEUKEMIC CHANGE IN WHOLE-BODY IRRADIATED RFM/UP ICE. (Eng.) Ludwig, F. C. (Coll. Medicine, Univ. f California, Irvine, Calif. 92664); Morat, M. M.; chug, W. G. *Proc. Soc. Exp. Biol. Med.* 148(2): 75-379; 1975.

188 MUTAGENICITY TEST OF IRRADIATED TEST ANIMAL FEED IN "HOST-MEDIATED ASSAY" WITH ALMONELLA TYPHIMURIUM G 46. (Ger.) Münzner, R. Bundesforschungsanstalt für Ernährung, Institut ür Strahlentechnologie, D-75 Karlsruhe, Engesser-trasse 20, Bundesrepublik Deutschland); Renner, . W. *Int. J. Radiat. Biol.* 27(4):371-375; 1975.

189 MEASUREMENT OF DIVISION DELAY AFTER X-RAY DOSES OF 20 RADS OR LESS AND THE EFFECT F CYCLOHEXIMIDE ON THE EXPRESSION OF DIVISION DE-AY AFTER LOW DOSE INJURY [abstract]. (Eng.) chneiderman, M. H. (Battelle, Pac. Northwest Lab., ichland, Wash.). *Radiat. Res.* 62(3):537; 1975.

190 LARVAL GANGLIA OF *DROSOPHILA M.* AS A NEW TEST SYSTEM FOR THE STUDY *IN VIVO* OF NDUCED CHROMOSOME ABERRATIONS. (Eng.) Gatti, M. Centro di Genetica Evoluzionistica del CNR, Isti-uto di Genetica, Rome (Italy)); Tanzarella, C.; impinelli, S.; de Marco, A. *Mutat. Res.* 29(2): 51; 1975.

191 X-RAY-INDUCED CHROMOSOME ABERRATIONS IN OOCYTES OF MICE. I. DOSE-DEPENDENT CHROM-SOME ABERRATIONS IN OVULATED OOCYTES AFTER IRRADIA-ION OF THE PRE-OVULATORY PHASE. (Eng.) Reichert, . (Institut Für Anthropologie und Humangenetik der niversität Heidelberg, Neuenheimerfeld 328, West ermany); Hansmann, I.; Röhrborn, G. *Mutat. Res.* 9(2):217; 1975.

3192 ACUTE GRANULOCYTIC LEUKEMIA IN HODGKIN's DISEASE. (Eng.) Raich, P. C. (Univ. of Wisconsin Medical Center, 1300 University Ave., Madison, Wis. 53706); Carr, R. M.; Meisner, L. F.; Korst, D. R. *Am. J. Med. Sci.* 269(2):237-241; 1975.

3193 ENVIRONMENTAL MUTAGENS AND ENVIRONMENTAL FACTORS THAT CAN MODIFY THEIR ACTION. (Eng.) de Marco, A. (Centro Genetica Evoluzionis-tica del CNR, Istituto di Genetica, Rome (Italy)); Belloni, M. P.; Cozzi, R.; Olivieri, G. *Mutat. Res.* 29(2):253; 1975.

3194 DOSIMETRIC SIGNIFICANCE OF CYTOGENIC TESTS IN ACCIDENTALLY IRRADIATED SUBJECTS. (Fre.) Doloy-Biola, M. T. (Département de protec-tion, CEN de Fontenay-aux-Roses., FRANCE); Le Go, R.; Ducatez, G.; Lepetit, J.; Bourguignon, M. *Bull Inf. Sci. Techn. Comm. Energ. Atom.* (203):17-25; 1975.

3195 RADIATION-INDUCED INTESTINAL TUMORS IN RATS: CORRELATION BETWEEN THE AMOUNT OF THE CIRCULATING TUMOR-RELATED ANTIGEN(S) AND TUMOR SIZES [abstract]. (Eng.) Cheng, H. F. (Radiat. Res. Lab. Univ. Iowa, Iowa City); Cantarero, L.; Osborne, J. W. *Radiat. Res.* 62(3):604; 1975.

See also:

* (Rev): 3005, 3009, 3036, 3048, 3049, 3050, 3051
* (Viral): 3229, 3249
* (Path): 3456

3196 THE LOCATION OF THE GENES CODING FOR HEXON AND FIBER PROTEINS IN ADENOVIRUS DNA.
(Eng.) Mautner, V. (Natl. Inst. Med. Res., London, England); Williams, J.; Sambrook, J.; Sharp, P. A.; Grodzicker, T. *Cell* 5(1):93-99; 1975.

A serological analysis was performed of the structural proteins of 17 adenovirus recombinants that permitted the genes coding for two of the chief components of the virus capsid (hexon and fiber) to be assigned to precise locations on the genetic and physical maps of adenovirus DNA. High titer stocks of recombinants and the parental, wild-type viruses were prepared in monolayers of HeLa cells. For complement-fixation assays, 10^7 cells were removed three days after infection, resuspended in 1 ml of infection medium, and sonicated. The aqueous layer after centrifugation contained approximately 10^9 plaque-forming U/ml, and was used at a dilution of 1:20 in complement fixation tests. For gel diffusion experiments, 10^6 infected cells were resuspended in 0.2 ml of phosphate-buffered saline and disrupted in an ultrasonic bath for two minutes. Hexon and fiber of AD2 and AD5 were prepared from soluble cell extracts of infected HeLa cells and purified by DEAE cellulose chromatography and crystallization. Antisera to these antigens were raised in guinea pigs. The phenotype of the recombinants was determined by the serological analysis. By correlating this data with the genetic and physical maps of the adenovirus genome, obtained by recombination and restriction endonuclease analysis, the genes coding for the hexon and fiber were assigned to specific locations on the adenovirus DNA. It is concluded that the region of adenovirus DNA that codes for fiber protein lies towards the right hand end of the genome between positions 0.85 and 0.98; this corresponds to a DNA fragment of about 2.7×10^6 daltons, with the coding potential for a protein of 99,000 daltons. It is also concluded that the segment of DNA that codes for hexon lies between positions 0.44 and 0.59, corresponding to a DNA fragment of 3.0×10^6 daltons, with the coding potential for a protein of 130,000 daltons.

3197 ADENOVIRUS-2 mRNA IS TRANSCRIBED AS PART OF A HIGH-MOLECULAR WEIGHT PRECURSOR RNA.
(Eng.) Bachenheimer, S. (Rockefeller Univ., New York, N.Y. 10021); Darnell, J. E. *Proc. Natl. Acad. Sci. USA* 72(11):4445-4449; 1975.

The order of transcription and the length of nascent RNA transcripts from adenovirus-2 (Ad-2) DNA in the nucleus of infected cells were investigated. The growing RNA chains were labeled with [^{3}H]uridine for 1 or 2 min. The RNA was separated on the basis of size, and to the ordered *Eco*R1 restriction endonuclease fragments derived from Ad-2 DNA. The majority of the virus-specific RNA molecules were synthesized as very high-molecular-weight units beginning at a common point at least 25-30,000 base pairs from one end of the Ad-2 DNA. These molecules could be reduced in size without further RNA synthesis. The experiments indicate the obligatory origin of Ad-2 messenger RNA from a high-molecular-weight precursor molecule.

3198 PHYSICAL MAP AND STRAND POLARITY OF SPECIFIC FRAGMENTS OF ADENOVIRUS-ASSOCIATED VIRUS DNA PRODUCED BY ENDONUCLEASE R·*Eco*RI. (Eng.) Carter, B. J. (Natl. Inst. Arthritis, Metabolism and Digestive Diseases, Bethesda, Md. 20014); Khoury, G.; Denhardt, D. T. *J. Virol.* 16(3):559-568; 1975.

Experiments designed to determine the physical order and strand polarity of the fragments derived from adenovirus-associated virus type 2 (AAV2) DNA duplexes by cleavage with restriction endonuclease R·*Eco*RI are described. Cleavage of AAV2 DNA linear duplex monomers with the restriction endonuclease yielded three fragments, A, B, and C, having approximate molecular weights of 1.6×10^6, 1.1×10^6, and 1.3×10^5, respectively. Radioactive labeling the 5' termini of AAV DNA before cleavage with R·*Eco*RI showed that A and B were terminal fragments and C was internal. Separation of the complementary strands of fragments A and B showed that A contained the 5' terminus of the minus strand and the 3' terminus of the plus strand, and conversely for fragment B. The physical map of the AAV R·*Eco*RI fragments could thus be unambiguously determined and was drawn with B at the left-hand and A at the right-hand end. On this map, transcription of stable AAV messenger RNA from the minus strand proceeded from left to right, beginning in fragment B and terminating in fragment A. The asymmetry in distribution of thymidine between the AAV DNA plus and minus strands was preferentially located in fragment A, which represented the right-hand half of the duplex molecule. These experiments enable preparative separation of all four single-strand termini of AAV DNA and provide a basis for orientation of fragment maps derived by cleavage with other restriction enzymes.

3199 CLEAVAGE OF ADENOVIRUS-5 DNA BY AN ENDONUCLEASE FROM *HAEMOPHILUS PARAINFLUENZAE*.
(Eng.) Kozlov, J. V. (Norsk Hydro's Inst. for Cancer Res., Montebello, Oslo, Norway); Olsnes, S.; Brogger, A.; Pihl, A. *FEBS Lett.* 57(2):153-157; 1975.

The fragments obtained by cleavage of adenovirus type 5 (ad-5) with an endonuclease (Hpal) from *Haemophilus parainfluenzae* were mapped. Agarose gel (1 and 2% agarose) electrophoresis of Ad-5 DNA cleaved with [^{3}H]Hpal endonuclease yielded seven fragments that were designated alphabetically in order of decreasing molecular weight. Fragments D and E were the terminal fragments as shown by labeling of the 3'-terminal ends of Ad-5 with terminal nucleotidyl transferase. The three fragments, A, B, and C, obtained by cleavage of Ad-5 DNA with EcoRi restriction endonuclease were used for further localization of the Hpal fragments in the intact DNA. The total sequence of the Hpal fragments was shown to be E-C-G-A-B-F-D. According to published data, the minimal part of the Ad-5 genome capable of inducing transformation is between 1-6% from the left end of the molecule. The terminal fragment obtained from the left end of Ad-5 DNA by cleavage with Hpal (fragment E) was 4.2% of the genome.

00 SOME PROPERTIES OF ADENOVIRUS 12-INDUCED TRANSPLANTATION ANTIGEN, AS MEASURED BY THE CROPHAGE MIGRATION INHIBITION TEST. (Eng.) Potter, W. (Univ. Sheffield Med. Sch., England); Rees, R. *Eur. J. Cancer* 11(5):335-341; 1975.

udies were carried out to determine if the macro-age migration inhibition test could be used to say adenovirus 12-induced transplantation anti-n(s). Cell-free extracts of transplanted adeno-rus 12-induced tumors of CBA mice stimulated macro-age migration inhibition factor (MIF) from spleen lls from CBA mice previously immunized with the tracts. Using this test to assay transplantation tigen present in the tumor extracts, the antigens re found to be resistant to heating at 56 C for o hours and to three extractions with ether. They re not precipitated by dialysis at pH 5.0 or 6.0 contrast, the antigens were destroyed by sodium oxycholate and sodium dodecyl sulfate and by di-ysis at pH 4.0. The antigen could not be recovered om the precipitate formed by this last treatment. ese properties were similar to those previously termined using the transplantation immunity test to say for antigen. The sole exception was that ex-acts dialysed at pH 5.0 were able to stimulate MIF, t did not immunize mice against tumor challenge. e results indicate that the two tests measure the me antigen, and that the macrophage migration in-bition test is a more practical assay to monitor e purification and determine the properties of enovirus 12-induced transplantation antigen(s).

01 ISOENZYMES OF LACTATE- AND MALATE-DEHYDRO-GENASES IN NUCLEI OF RAT EMBRYO FIBRO-ASTS INFECTED WITH ONCOGENIC ADENOVIRUS TYPE 12. us.) Ageenko, A. I. (P. A. Gertsen Moscow Sci. s. Inst. Oncol., USSR); Vitorgan, Yu. E. *Vopr. rusol.* (2):159-163; 1975.

e spectra and electrophoretic motility of lactate hydrogenase (LDH) and malate dehydrogenase (MDH) oenzymes were studied in nuclei of rat embryo broblasts infected with oncogenic adenovirus type . Monolayers of murine embryonal fibroblast cells re infected with the virus on the third day of ltivation, and were investigated on the 3rd, 5th, h, 18th, and 24th days of incubation. Proteins re fractionated by disc-electrophoresis in poly-rylamide gel. Three LDH isoenzymes were found in e globulin fraction of the nuclei in control and perimental cultures during the first 18 days. Two oenzymes; LDH_1 with a relative electrophoretic tility of 0.008, and LDH_2 with a motility of 0.08, th characteristic for aerobic glycolysis, were und on the 24th day in the infected cultures. e LDH activity was statistically significantly creased in the infected cultures on the 5th and th days. The LDH_1 activity was 167 ± 10 on the fth day, and 109 ± 8 mm^2 on the 18th day in the ntrol, against 198 ± 2.8 mm^2 and 179.8 ± 18 mm^2 in e infected cultures. The LDH_2 activity was ± 3.5 mm^2 against 40 ± 8.5 mm^2 in the control on e 24th day. The electrophoretic motility of H_1 slightly increased by the fifth day and decreased by the 18th day, while that of LDH_2 showed a sharp decrease by the 24th day. The motility of LDH_3 increased by the 18th day. The MDH_1 activity was significantly increased on the 5th and 18th day, the MDH_2 activities were increased on the 3rd, 5th, and 8th days, and the MDH_3 activity was increased on the third and 24th days. The electrophoretic motility of LDH_3 was significantly increased on the 5th and 8th days. The findings indicate that the partial morphological transformation, starting on about the 18th day, was accompanied by an increased LDH_1 and LDH_2 activity, followed by a drop in the LDH_1 activity, and by sharp changes in the MDH_3 activity. The changes observed in the isoenzyme synthesis are probably due to the epigenomic effect of oncovirus and may be used as indicators of the malignant transformation of tissue cultures.

3202 CONTROL OF NUCLEAR DIVISION IN SV40 AND ADENOVIRUS TYPE 12 TRANSFORMED MOUSE 3T3 CELLS. (Eng.) O'Neill, F. J. (Univ. Utah Med. Cent., Salt Lake City). *Int. J. Cancer* 15(5):715-723; 1975.

The control of nuclear division was investigated in simian virus 40 (SV40) and adenovirus type 12 (Ad-12)-transformed cells. The cells included BALB/c 3T3 cells, Swiss 3T3 cells (3T34E), BALB/c mouse embryo fibroblasts (MEF), and SVT2 cells (SV40-transformed Swiss-Webster mouse cells). The formation of multinuclear cells and premature chromosome condensation (PCC) was studied following incubation for seven days with 1.5 μg/ml cytochalasin B (CB). MEF and both BALB/c 3T3 and 3T34E cells became binucleated in the presence of CB and cells with three or more nuclei were very rare or undetectable. Transformation of MEF by SV40 produced a dramatic change in response to CB. These cells, which contain SV40 T-antigen, became highly multinucleated in the presence of CB. More than 20% of the cells had at least seven nuclei. PCC were frequent and occurred in at least 10% of mitoses. SV40 MEF were diploid or tetraploid. Transformation of 3T3 by SV40 or adenovirus type 12 did not result in a marked change in the response to CB. Although some trinucleate and tetranucleate cells were formed, cells with more nuclei were undetectable or rare. PCC were also rare. These cells showed chromosome numbers somewhat lower than their untransformed parents and in one line the chromosome number appeared to decrease with the passage of the cells. This failure to undergo a marked change in responsiveness to CB following transformation was not a characteristic of all transformed 3T3 cells. SVT2, a line of 3T3 which was transformed by SV40 prior to its establishment as a continuous line, responded to CB with a high degree of multinucleation. Because 3T3, 3T34E and their transformed derivatives were aneuploid or subtetraploid, an association must exist between chromosomal constitution and control of nuclear division. The transformed MEF and the SVT2 cells were diploid or near diploid. The results suggest that 3T3 and 3T34E may be constitutive for control of nuclear division because transformation does not result in loss of controlled nuclear division.

3203 DEMONSTRATION OF INFECTIOUS DNA IN TRANSFORMED CELLS: III. CORRELATION OF DETECTION OF INFECTIOUS DNA-PROTEIN COMPLEXES WITH PERSISTENCE OF VIRUS IN SIMIAN ADENOVIRUS SA7-INDUCED TUMOR CELLS. (Eng.) Butel, J. S. (Baylor Coll. Medicine, Houston, Tex. 77025); Talas, M.; Ugur, J.; Melnick, J. L. *Intervirology* 5(1/2):43-56; 1975.

Primary tumors induced in newborn hamsters by simian adenovirus SA7 were investigated in transfection experiments. The animals were injected sc with SA7 virus (5 x 10^7 plaque-forming units/0.1 ml) within 24 hr after birth. Infectious DNA-protein complexes were readily detected in both the supernatant and pellet fractions obtained by a modified Hirt extraction procedure; DEAE-dextran was required for infectivity to become manifest. Infectivity could be abolished by exposure to DNase (100 μg/ml), but it was unaffected by SA7-specific antiserum or RNase (50 μg/ml), and only partially inactivated by trypsin (300 μg/ml) treatment. SA7 tumor cells serially passaged either in tissue culture or in hamsters yielded infectious DNA complexes much less frequently and appeared to evolve into nonyielder cell lines. When large numbers of cells were lysed, intact virus could be recovered from all the primary tumors and from some of the subcultured cell lines. There was a correlation between the persistence of complete virus and the presence of infectious DNA-protein complexes. When the tumor cells carried very small amounts of intact virus, infectious DNA complexes could still be detected; when virus could no longer be detected in the tumor cells, infectious DNA complexes could no longer be found. The results suggest that a portion of the infectious DNA moieties exists as viral DNA-protein complexes in the tumor cells.

3204 DIFFERENT HEMATOLOGICAL DISEASES INDUCED BY TYPE C VIRUSES CHEMICALLY ACTIVATED FROM EMBRYO CELLS OF DIFFERENT MOUSE STRAINS. (Eng.) Greenberger, J. S. (Natl. Cancer Inst., Bethesda, Md.); Stephenson, J. R.; Moloney, W. C.; Aaronson, S. A. *Cancer Res.* 35(1):245-252; 1975.

The biological activities of two endogenous type C viruses chemically induced from C58-derived and BALB/c mouse embryo cells in culture were compared in NIH Swiss mice. Preparations of BALB:virus-1 and murine leukemia virus C58 (C58-MuLV) were tested for the major mouse type C virion polypeptide (*p*30) and for infectivity for NIH/3T3 and BALB/3T3 cells by the polymerase induction assay. Each virus was more infectious for NIH/3T3, and C58-MuLV was about 10-fold more infectious per nanogram *p*30 than the BALB/virus-1. Infectious type C virus recovery from spleens of NIH Swiss mice inoculated at birth with 10^5 polymerase-inducing units of either virus or serum-free medium were assayed after incubation for 14 days at 37 C. At 15 mo postinoculation, all mice inoculated with BALB:virus-1 and all of those inoculated with C58-MuLV were virus-positive. A quantitative comparison was made of virus production by mouse spleens ten months after inoculation. The level of virus produced by spleens of C58-MuLV-inoculated mice was much higher than that of spleens releasing BALB:virus-1. Virus inoculation led to the development of diseases associated with splenomegaly in 19 of 135 C58-MuLV-inoculated mice and 16 of 100 BALB:virus-1 inoculated mice. Lymphoadenopathy also occurred in virus-inoculated mice. Histopathological diagnosis in the C58-MuLV group was lymphoblastic leukemia, compared to the myeloid metaplasia or myelogenous leukemia found in the BALB:virus-1 group. These data indicate that two distinct diseases were induced *in vivo* by each endogenous type C virus. It is also suggested that the N-tropic endogenous C58 virus is the causative agent in naturally occurring leukemia in this strain.

3205 PRIMATE TYPE C VIRUS p30 ANTIGEN IN CELLS FROM HUMANS WITH ACUTE LEUKEMIA. (Eng.) Sherr, C. J. (Natl. Cancer Inst., Bethesda, Md.); Todaro, G. J. *Science* 187(4179):855-857; 1975.

The peripheral blood WBC of patients with acute leukemia were studied for the presence of type C virus p30 antigen. The WBC were obtained from five patients by leukophoresis, and were extracted and partially purified by gel filtration. The extracts were used as competing antigens in radioimmunoassays for the p30 proteins of wooly monkey type C virus (SSAV), gibbon age leukemia virus (GALV), feline leukemia virus (FeLV), Rauscher murine leukemia virus (MuLV), and an endogenous baboon type C virus (M7/M28 group). The assay showed little or no difference between SSAV and GALV p30 proteins, and did not detect those of other type C viral groups. Of the five extracts from the patients tested, all competed for ^{125}I-labeled p30 protein of SSAV. None competed for the p30 protein of MuLV or FeLV. Control studies with other assays for p30 proteins of SSAV and GALV showed that the competition reactions of the SSAV assay are independent of the source or manner of purification of the labeled test antigens, the antisera used, or the sensitivities of the assays. All five assays showed comparable antigen levels (2-20 ng/mg tissue). It is concluded that viruses of this group may be associated with acute leu kemia in man.

3206 INDUCTION OF MOUSE TYPE-C VIRUS BY LIPOPOLYSACCHARIDE. (Eng.) Greenberger, J. S (Natl. Cancer Inst., Bethesda, Md.); Phillips, S. M. Stephenson, J. R.; Aaronson, S. A. *J Immunol.* 115 (1):317-320; 1975.

The effects of lymphocyte mitogens and halogenated pyrimidines on the induction of specific endogenous viruses from BALB/c mouse spleen cells were compared A cocultivation technique was used to quantitate type-C virus release from BALB/c embryo fibroblasts and spleen cells. NIH/3T3 and NRK cell lines, nonproductively transformed by the Kirsten strain of murine sarcoma virus, were used. KIMSV nonproducer lines of NIH/3T3 and NRK (K-NIH and K-NRK, respectively) were plated at 3 x 10^6 cells per Petri dish. Sarcoma virus release by either K-NIH or K-NRK cells cocultivated with untreated BALB/c spleen cells was below the level of detection. Spleen cells exposed

iododeoxyuridine (15 μ/ml, 12 hr) and cocultivated n K-NIH (21 days) yielded N-tropic virus at a er of $10^{2.7}$ focus-forming units/ml, in high ex- s of virus infectious for NRK cells. When the e iododeoxyuridine-induced spleen cells were cul- ed with K-NRK, there was also growth of virus; ever, this virus was preferentially infectious NRK cells, and was revealed by radioimmunoassay be of mouse origin. Spleen cells exposed to lipo- ysaccharide (50 μg/ml, 48 hr) released type-C us that grew in K-NRK cells but not in K-NIH ls. The NRK-tropic virus activated from lipo- ysaccharide-treated spleen cultures titered n $10^{2.3}$ to $10^{2.8}$ focus-forming units/ml. The e cultures, exposed to 10 μg/ml concanavalin A 48 hr, titered from $10^{1.3}$ to $10^{1.6}$ focus-forming ts/ml. The relative differences in the frequency virus activation in response to lipopolysaccharide concanavalin A were constant findings. Radio- unoassays for mouse type-C virus p30 showed that opolysaccharide- and concanavalin A-activated uses were of mouse origin. It is concluded that opolysaccharide causes selective release of a otropic type-C virus endogenous to BALB/c mouse een cells. The finding that blastogenesis as a ction of lipopolysaccharide concentration cor- ates with the level of virus activation is con- tent with the hypothesis that blast transforma- n of this cell type is involved in xenotropic us induction.

TYPE-C VIRUS-SPECIFIC NUCLEIC ACID SEQUENCES IN CULTURED RAT CELLS. (Eng.) Tsuchi- N. (Flow Lab., Inc., Rockville, Md. 20852); Gil- , R. V.; Hatanaka, M.; Freedman, A. E.; Huebner, J. *Int. J. Cancer* 15(1):109-115; 1975.

e-C virus-specific nucleic acid sequences were died in cultured rat control cells as well as in nsformed cells. The cell lines used were low- sage Fischer rat embryo cells treated variously h 3-methylcholanthrene (0.5-1.0 μg/ml) or 5- mo-2'-deoxyuridine (20 μg/ml) or a dual treatment. -percent cell suspensions in Tris-sodium dodecyl fate buffer were treated with pronase (100 μg/ml, hr, 37 C) and extracted sequentially with equal umes of Tris-saturated phenol and chloroform- amylalcohol. The aqueous phase was removed, and was precipitated with ethanol. DNA was dis- ved in 0.1 x SSC (0.5 M NaCl, 0.015 M Na rate), sonicated for 5 min and treated with se. The extraction procedure was repeated once. l RNA was extracted by the hot phenol method and ther purified by centrifugation. The reaction tures (generally 5 ml of purified virus) for ob- ning complementary viral DNA contained 0.1 M cine-NaOH buffer; 10 mM dithiothreitol; 0.05 mM P, dGTP, dCTP; 1.25 mCi of ^{3}H-TTP; 0.03 M NaCl; M $MnCl_2$; 0.01% NP-40 and 100 μg/ml actinomycin The mixtures were incubated overnight. The cific activity of the DNA transcripts averaged 10^7 CPM/μg. Hybridization of ^{3}H-viral comple- tary DNA to cell DNA was performed in 2 x SSC 66 C for varying periods of time. Cell DNA was sent in about 4 x 10^5-fold weight excess. Hy- dization was determined by resistance of labeled DNA to the S-1 nuclease from *Aspergillus oryzea*. Single-stranded DNA transcripts of the rat type-C viruses hybridized specifically to DNA of several rat cell cultures with no obvious qualitative or quantitative differences. Similar products prepared from a pseudo-type sarcoma virus with contributions from rat and mouse type-C viruses hybridized to both rat and mouse cellular DNA; mouse viral transcripts did not hybridize to rat cell DNA. Viral RNA was detected in all rat cells by means of the rat viral DNA transcripts, with some differences between untreated low-passage cells and sister cultures treated with bromodeoxyuridine or bromodeoxyuridine plus methylcholanthrene. Cells treated with both compounds were previously shown to be transformed and tumorigenic, and these were distinguishable by kinetic analysis form the control cells. It is concluded that the genome of rat type-C viruses is represented, at least in part, in the DNA of normal rat cells.

3208 SEROEPIDEMIOLOGICAL EVIDENCE FOR HORIZONTAL TRANSMISSION OF BOVINE C-TYPE VIRUS. (Eng.) Piper, C. E. (Sch. Veterinary Medicine, Univ. Pennsylvania, Kennett Square, Pa. 19348); Abt, D. A.; Ferrer, J. F.; Marshak, R. R. *Cancer Res.* 35(10): 2714-2716; 1975.

Studies were performed to determine the natural mode of transmission of bovine C-type virus (BLV). Thirty colostrum-deprived calves from leukemia-free herds were foster nursed for ten weeks on cows infected with BLV from multiple-case herds or on cows from leukemia-free herds. After weaning, the calves were raised in continuous contact with BLV-infected animals of approximately the same ages. Sera collected at 6-18 and 43-48 mo of age were examined for the presence of antibodies to BLV by the immunofluorescent antibody test. At 6-18 mo of age, only one of the 30 calves from leukemia-free herds had a detectable antibody response to BLV. By 43-48 mo of age the number of antibody-positive animals had risen to 17. The foster dam's herd of origin did not significantly affect the rate of BLV infection. These results indicate that BLV can be horizontally transmitted from infected to noninfected animals.

3209 VERTICAL TRANSMISSION OF C-TYPE VIRUSES: THEIR PRESENCE IN BABOON FOLLICULAR OOCYTES AND TUBAL OVA. (Eng.) Kalter, S. S. (Microbiology and Infectious Diseases, Southwest Foundation Res. and Education, San Antonio, Tex. 78284); Heberling, R. L.; Smith, G. C.; Panigel, M.; Kraemer, D. C.; Helmke, R. J.; Hellman, A. *J. Natl. Cancer Inst.* 54(5):1173-1176; 1975.

The follicular oocytes and tubal ova of baboons were studied by electron microscopy to detect C-type virus particles; the presence of such particles would support the hypothesis that either a provirus or virogene-oncogene, or viral information rather than an intact virus acts as a mechanism for inheritance of the oncogenic potential vertically. C-type particles were found in follicular oocytes from 5 of 7 baboons and in tubal ova from 2 of 5 animals. Typ-

ically, these particles were adjacent to the plasma membrane in the perivitelline space or along the inner margin of the zona pellucida. The particles were present in both atretic and nonatretic oocytes. No intracytoplasmic or intracisternal A-type particles were observed in follicular cells surrounding the follicular oocytes or in any other ovarian structures. Thus, these C-type viruses may be of germ-cell origin. These findings support the concept of vertical transmission of C-type particles.

3210 LOCALIZATION AND QUANTITATION OF EBV-ASSOCIATED NUCLEAR ANTIGEN (EBNA) IN RAJI CELLS. (Eng.) Bahr, G. F. (Armed Forces Inst. Pathology, Washington, D. C., 20306); Mikel, U.; Klein, G. *Beitr. Pathol.* 155(1):72-78; 1975.

The direct localization of Epstein-Barr virus (EBV)-associated nuclear antigen (EBNA) in Raji cells was studied *via* electron microscopy. In experiments employing ferritin-labeled goat antihuman antibody, β_{1C}, no meaningful results were obtained; both positive and negative serum, and unreacted chromatin bound diffusely and in patches. An immunocytochemical method involving a horseradish-peroxidase labeling technique showed a strong reaction on and along every chromatin fibril. This process resulted in encrustation and caking of chromatin strands when positive anti-EBNA serum was used. The sensitivity of the method was tested by a quantitative analysis of the electron microscopic material, based on the relation of contrast and object dry mass. The dry mass of Raji chromatin increased after exposure to both EBV-negative and -positive serum, most significantly with the latter; osmium tetroxide produced a 15% decrease in mass. It is concluded that the complement-fixing EBV-associated antigen is widely distributed throughout the nucleus. It occurs on chromatin fibers at sites so close to each other that available immunocytochemical techniques cannot distinguish them.

3211 STUDIES ON THE PRESENCE OF ANTIBODIES TO EB VIRUS AND OTHER HERPESVIRUSES IN NORMAL CHILDREN AND IN INFECTIOUS MONONUCLEOSIS. (Eng.) Gergely, L. (Univ. Med. Sch., Debrecen, Hungary); Czeglédy, J.; Váczi, L.; Szabó, B.; Binder, L.; Szalka, A. *Acta Microbiol. Acad. Sci. Hung.* 22(2): 75-82; 1975.

The frequency of antibodies to Epstein-Barr virus and of antibodies to herpes simplex virus and cytomegalovirus were studied in children and in patients with infectious mononucleosis. The sera of 100 Hungarian children free from infectious disease were examined by indirect immunofluorescence for the presence of antibodies to Epstein-Barr virus. The sera of 46% of the children in their first year of life was positive. The corresponding value for children 2-6 yr old was 66%, and 91% for children aged 7-14 yr. The percentage of subjects with antibodies to cytomegalovirus and herpes simplex virus was about 50%, irrespective of age. Serum samples from 69 patients with infectious mononucleosis were also tested. It was found that in the Paul-Bunnell-positive cases the anti-Epstein-Barr virus antibodies tended to be dominant, whereas antibodies to cytomegalovirus tended to be dominant in the Paul-Bunnell-negative cases. The data support the concept of an etiological role of cytomegalovirus in some Paul-Bunnell-negative cases of infectious mononucleosis, but fail to demonstrate a consistent relationship between Epstein-Barr virus and the disease.

3212 ANTIBODY PATTERNS TO HERPESVIRUSES IN KAPOSI'S SARCOMA: SEROLOGICAL ASSOCIATION OF EUROPEAN KAPOSI'S SARCOMA WITH CYTOMEGALOVIRUS. (Eng.) Giraldo, G. (Mem. Sloan-Kettering Cancer Cent., New York, N.Y.); Beth, E.; Kourilsky, F. M.; Henle, W.; Henle, G.; Mike, V.; Huraux, J. M.; Anderson, H. K.; Gharbi, M. R.; Kyalwazi, S. K.; Puissant, A. *Int. J. Cancer* 15(5):839-848; 1975.

Sera from 16 European and 48 African patients with Kaposi's sarcoma (KS) were examined for antibody titers to cytomegalovirus (CMV), Epstein-Barr virus (EBV) and herpes simplex virus (HSV) types 1 and 2 by indirect hemagglutination, complement fixation, virus neutralization, and indirect immunofluorescence The patients were classified, according to the stage of disease, as progressive and regressive. Control sera were obtained from healthy adults, matched for age, sex, race, socioeconomic status and geographic location, as well as from patients with melanoma, some of whom were receiving chemotherapy, similar to that given to the KS patients. All KS sera contained CMV-neutralizing antibodies. Of the European patient mainly regressors, 75% showed elevated anti-CMV titer by indirect hemagglutination with a significant increase in the geometric mean over the corresponding healthy adult group and the melanoma group. An overrepresentation of high anti-CMV titers, although less marked, was found by complement fixation. There was no significant association with antibodies to EBV, HSV-1 and HSV-2 related antigens. By contrast, the African KS patients, mainly progressors, did not show a serologic association with CMV or with EBV and HSV-1 and 2. It is suggested that CMV may be involved in human malignancy such as KS, although such a role cannot be established by serologic evidence alone.

3213 MITOCHONDRIAL AND HERPESVIRUS-SPECIFIC DEOXYPYRIMIDINE KINASES. (Eng.) Leung, W. -C. (Baylor Coll. Medicine, Houston, Tex. 77025); Dubbs, D. R.; Trkula, D.; Kit*, S. *J. Virol.* 16(3): 486-497; 1975.

The thymidine (TdR) and deoxycytidine (CdR) kinase isozymes of uninfected and herpesvirus-infected cells were characterized and compared. The subcellular distribution of the isozymes was studied, and a specific assay for CdR kinase was devised. The TdR kinase isozymes were partially purified, and the purified enzymes were analyzed by disc polyacrylamide gel electrophoresis, isoelectric focusing, and glycerol gradient centrifugation and by substrate competition and dCTP inhibition studies. In the cytosol of uninfected mouse, chicken, and owl monkey kidney cells, two different proteins, TdR

ase F and Cdr kinase 2, catalyzed the phosphor-
tions of TdR and CdR, respectively. TdR kinase
id not phosphorylate CdR, nor did CdR kinase
hosphorylate TdR. A second TdR kinase isozyme
sent in HeLa(BU25) mitochondria (TdR kinase B)
o lacked CdR phosphorylating activity. In con-
st, a genetically distinctive deoxypyrimidine
ase (TdR kinase A) of mouse, human, and chick
ochondria catalyzed the phosphorylation of both
and CdR. Three herpesviruses, marmoset herpes-
us and herpes simplex virus types 1 and 2, in-
ed in the cytosol fraction of LM(TK⁻) mouse
ls isozymes that shared common properties with
ochondrial TdR kinase A, including the ability
catalyze the phosphorylation of both TdR and
. However, the herpesvirus-induced deoxypyri-
ine kinases differed from mitochondrial TdR
ase A with respect to sedimentation coefficient,
sitivity to dCTP inhibition, and antigenic deter-
ants. The herpesvirus-specific and the mito-
ndrial deoxypyrimidine kinases exhibited a pre-
ence for TdR over CdR as nucleoside acceptor.
udorabies virus and herpesvirus of turkeys in-
ed cytosol TdR kinases resembling the other
pesvirus-induced TdR kinases in several proper-
s, but like cellular TdR kinase F, the pseudo-
ies virus and herpesvirus of turkeys TdR kinases
ked detectable CdR phosphorylating activities.
ally, a marmoset herpesvirus mutant resistant
bromodeoxyuridine, equine herpesvirus type 1,
Herpesvirus aotus induced neither TdR nor CdR
sphorylating enzymes during productive infections.

4 ANATOMY OF HERPES SIMPLEX VIRUS DNA: EVIDENCE FOR FOUR POPULATIONS OF MOLE-
ES THAT DIFFER IN THE RELATIVE ORIENTATIONS OF
IR LONG AND SHORT COMPONENTS. (Eng.) Hayward,
S. (Dept. Microbiology and Biophysics and Theo-
ical Biology, Univ. Chicago, Chicago, Ill.
37); Jacob, R. J.; Wadsworth, S. C.; Roizman, B.
c. *Natl. Acad. Sci. USA* 72(11):4243-4247; 1975.

anatomy of herpes simplex virus 1, human herpes
us 1 (HSV-1) DNA was studied using electropho-
ically separated *Hin*III and *Eco*RI fragments
m a limit digest of the ^{32}P-labeled DNA. Cleavage
HSV-1 DNA (strain MP) with the *Hin*III restriction
yme yielded 14 fragments with summed molecular
ghts of 160 x 10^6. Six "major" fragments occur-
once in every molecule in the population and
ounted for 60% of the genetic information. Four
nor" fragments were present in amounts equivalent
one copy for every two genomes (0.5 molar ratio)
the other four occurred only once in every four
ecules (0.25 molar ratio). The minor fragments
ld be arranged into four equimolar sets, each
h summed molecular weights that accounted for
remaining 40% of the genome. Treatment with
bda 5' exonuclease revealed that all molecules
tained 0.5 molar ratio fragments at both termini.
se observations and the results of similar anal-
s of the *Eco*RI and double *Hin*III/*Eco*RI digests
icate that there are four distinct structural
ms of HSV DNA, which differ only in the relative
entations of two subregions, designated *L* and *S*.
L and *S* segments consist of 82 and 18% of the
sequences, respectively, and each has inverted terminally redundant regions that correspond to the internal duplications observed by electron microscopy. The DNA from other strains of HSV-1 and 2 also consists of equal proportions of all four possible permutations of the *L* and *S* segments. These unusual features of HSV DNA molecules have novel implications with regard to the genetic map and the mode of replication and evolution of herpes simplex viruses.

3215 DNA SYNTHESIS AND DNA POLYMERASE ACTIVITY OF HERPES SIMPLEX VIRUS TYPE 1 TEMPERATURE-SENSITIVE MUTANTS. (Eng.) Aron, G. M. (Southwest Texas State Univ., Biology Dept., San Marcos, Tex. 78666); Purifoy, D. J. M.; Schaffer*, P. A. *J. Virol.* 16(3):498-507; 1975.

Fifteen temperature-sensitive mutants of herpes simplex virus type 1 were studied with regard to the relationship between their ability to synthesize viral DNA and to induce viral DNA polymerase (DP) activity at permissive (34 C) and nonpermissive (39 C) temperatures. Human embryonic lung cells were infected at a multiplicity of 5-10 plaque-forming units per cell with each mutant and with KOS strain virus as the wild-type. At 34 C, all mutants synthesized viral DNA while at 39 C four mutants demonstrated a DNA$^+$ phenotype, three were DNA$^\pm$, and eight were DNA$^-$. DNA$^+$ mutants induced levels of DP activity similar to those of the wild-type virus at both temperatures, and DNA$^\pm$ mutants induced reduced levels of DP activity at 39 C but not at 34 C. Among the DNA$^-$ mutants, three were DP$^+$, two were DP$^\pm$, and three showed reduced DP activity at 34 C with no DP activity at 39 C. DNA$^-$, DP$^-$ mutants induced the synthesis of a temperature-sensitive DP.

3216 SYNTHESIS OF PROTEINS IN CELLS INFECTED WITH HERPESVIRUS. X. PROTEINS EXCRETED BY CELLS INFECTED WITH HERPES SIMPLEX VIRUS, TYPES 1 AND 2. *(Eng.)* Kaplan, A. S. (Vanderbilt Univ. Sch. Med., Nashville, Tenn.); Erickson, J. S.; Ben-Porat, T. *Virology* 64(1):132-143, 1975.

The excretion of glycoproteins by cells infected with herpes simplex virus type 1 (HSV-9) and type 2 (HSV-2) were studied in primary monolayer cultures of rabbit kidney cells. In all experiments, rabbit cells were infected with approximately 10-20 plaque-forming U/cell. Radioactive labels included: [^{3}H]-L-leucine (46 Ci/mM); [^{14}C]glucosamine (1.8 Ci/mM); and 6-[^{3}H]glucosamine (12.6 Ci/mM). Antisera were prepared against excreted proteins and HSV virions. Polyacrylamide gel electrophoresis was used to assay profiles of the excreted glycoproteins. Electrophoretic profiles of glycoproteins excreted by infected and uninfected cells differed from those of cell-associated glycoproteins. Profiles of glycoproteins from HSV-1-infected cells differed from those excreted by HSV-2-infected cells, and both were unlike the profiles of glycoproteins excreted by uninfected cells. Indirect radioimmunoprecipitation showed that antisera against glycoproteins excreted by virus-infected cells were

highly type-specific. Serum prepared against type 1 (H_4) virions reacted significantly with cell-associated glycoproteins synthesized by cells infected with type 2 (333) virus, and precipitated 6.4% of the total glycoproteins. Less than 1% of these glycoproteins was precipitated by serum against H_4-excreted proteins. A small amount of glycoproteins excreted from HSV-infected cells reacted with heterologous antisera. Despite the differences in the amount of excreted proteins precipitated by homologous and by heterologous antisera, the proteins in both cases migrated similarly on electrophoresis. While major parts of proteins present in the excreted fraction were type-specific, a small amount of cross-reacting was present in these fractions. The nonspecific precipitates obtained with preimmune sera had featureless profiles. Serum prepared against H_4-excreted proteins neutralized 333 virus, but to a lesser extent than serum prepared against H_4-virus. The results demonstrate that glycoproteins are excreted from cells infected with both types of HSV and that these proteins are primarily specific for the herpes simplex virus type infecting cells.

3217 EFFECT OF ZINC IONS ON THE SYNTHESIS OF HERPES SIMPLEX VIRUS DNA IN INFECTED BSC-1 CELLS. (Eng.) Shlomai, J. (Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Asher, Y.; Gordon, Y. J.; Olshevsky, U.; Becker, Y. *Virology* 66(1):330-335; 1975.

The effect of zinc ions on the synthesis of herpes simplex virus (strain HF) DNA in infected BSC-1 cells was tested. At three hours postinfection, the cells were labeled with [^{3}H]thymidine in the absence or presence of $ZnSO_4$ at concentrations of 0.1, 0.2, and 0.3 mM. The cultures were harvested at 18 hr postinfection. $ZnSO_4$ (0.2 mM) inhibited the synthesis of viral DNA. A similar concentration of $ZnSO_4$ had no effect on DNA synthesis in uninfected cells. *In vitro* analyses revealed a marked depression of the DNA-polymerase activity in nuclei obtained from infected cells treated with 0.2 or 0.3 mM $ZnSO_4$, but not in cells treated with 0.1 mM $ZnSO_4$ during a 15-hr incubation. The results indicate that $ZnSO_4$ prevents the synthesis of HSV-DNA by a mechanism involving inhibition of the viral DNA polymerase activity.

3218 ANTIBODY TO HERPES SIMPLEX VIRUS TYPE 2-INDUCED NONSTRUCTURAL PROTEINS IN WOMEN WITH CERVICAL CANCER AND IN CONTROL GROUPS. (Eng.) Anzai, T. (Baylor Coll. Med., Houston, Tex.); Dreesman, G. R.; Courtney, R. J.; Adam, E.; Rawls, W. E.; Benyesh-Melnick, M. *J. Natl. Cancer Inst.* 54(5):1051-1059; 1975.

Sera of patients with cervical cancer and of control groups have been examined for the presence of antibodies of early proteins synthesized in herpes simplex virus type 2-infected cells. Sera from 15 control women, individually matched (age, race, socioeconomic status, sexual- and reproduction-associated factors) with 15 cervical cancer patients, as well as sera from ten patients with breast cancer were analyzed by an indirect radioimmune precipitation test followed by polyacrylamide gel electrophoretic analysis of immune precipitates. The relative reactivity to a major early nonstructural protein (VP134) was used to compare these selected sera. Approximately 90% of sera from patients with cervical cancer showed higher reactivity to VP134 than the mean of control sera, whereas 30% of sera from patients with breast cancer and less than 60% of sera from control women exceeded the mean value of control sera. The sera of all subjects had previously been tested for the presence of neutralizing antibodies to herpes simplex virus type 2, and it was found that serum reactivity to the protein was independent of the level of neutralizing antibodies. The authors discuss the need for more detailed information to determine if cervical cancer sera preferentially precipitate one or several herpes simplex virus-induced early proteins.

3219 SEROLOGICAL RELATIONSHIP BETWEEN A PATHOGENIC STRAIN OF MAREK'S DISEASE VIRUS, ITS ATTENUATED DERIVATIVE AND HERPES VIRUS OF TURKEYS (Eng.) Ross, L. J. N. (Houghton Poultry Res. Station Houghton, U.K.); Basarab, O.; Walker, D. J.; Whitby, B. *J. Gen. Virol.* 28(1):37-47; 1975.

The serological relationship between a pathogenic strain of Marek's disease virus (MDV), its attenuated derivative and Herpes virus of turkeys (HVI) was studied using precipitating antigens (A, B, and C) as references. Precipitating antigens present in extracts of chick embryo cells infected with the HPRS-16-attenuated strain (HPRS-16/att) of MDV were separated by gel filtration on Sephadex G200, and some of their properties were determined. The two main antigens detected with convalescent MDV serum, referred to as 'B' and 'C' antigens, had mobilities of 0·55 and 0·25, respectively, relative to phenol red on electrophoresis in 7·5% acrylamide gel. The B antigen was relatively stable and of low molecular weight in comparison with the C antigen. B and C antigens were in some instances also detected in culture medium of infected cells, but were distinguishable from the A antigen, a major glycoprotein antigen released into the culture medium of cells infected with HPRS-16. The results of immunodiffusion studies suggested that B antigen is common to MDV and strains of herpes virus of turkeys (HVT), and that at least two antigens (including C) are MDV-specific. The A antigen was also common to MDV and HVT strains. However, that the capacity of HPRS-16/att to synthesize A antigen was considerably reduced in comparison with HPRS-16 and HVT strains, and in some preparations the A antigen could not be detected. Evidence was also obtained for the presence of HVT-specific antigens associated mainly with the cell fraction.

3220 IODINATION OF HERPESVIRUS NUCLEIC ACIDS. (Eng.) Shaw, J. E. (Sch. Medicine, Univ. North Carolina, Chapel Hill, N.C. 27514); Huang, E. S.; Pagano, J. S. *J. Virol.* 16(1):132-140; 1975.

A simple procedure for the iodination of herpes simplex virus (HSV) DNA of high specific activity is presented. Strain 196 of herpes simplex type 2 was

pagated in human epidermoid cells (HEp-2). The cedure involves synthesis of ^{125}I-labeled 5-Iodo-P, which is subsequently used as a precursor for *in vitro* repair synthesis of HSV DNA. 5-Iodo-P is purified from the iodination reaction mix-e by anion exchange on DEAE cellulose; this purity checked by polyethyleneimine (PEI)-cellulose thin-er chromatography. ^{125}I-labeled HSV DNA is then thesized, with specific activity estimated as x 10^8 and 1.7 x 10^8 counts/min/μg. The iodinated DNA is purified by Sephadex gel filtration, and average buoyant density of 1.724 g/ml correlated l with that reported for uniodinated viral DNA 728 g/ml). Iodinated DNA was resistant to S_1-onuclease digestion in the native form, but was ceptible when denatured. Reassociation kinetics ^{125}I-labeled HSV DNA, in the presence of DNA ex-cted from HSV-infected or mock-infected HEp-2 ls, indicated that 20% and 88% of the iodinated had reassociated, respectively. ^{125}I-labeled odo-dCTP was prepared and used to synthesize omegalovirus (CMV) complementary RNA (cRNA). The A was highly sensitive to RNase activity, and ex-ited a linear reassociation relation to CMV DNA. inated cRNA was used as a probe to localize CMV in kidney tissue. The presence of grains was ealed considerably earlier than by ^{3}H-labeled A; that the grains produced were four times t produced by ^{3}H disintegration suggests some s in resolution. This method should be of value the preparation of viral probes, and for use autoradiography of viral nucleic acids.

1 MORPHOGENESIS OF MAREK'S DISEASE VIRUS IN FEATHER FOLLICLE EPITHELIUM. (Eng.) nson, E. A. (Dept. Pathobiol., Univ. Connecticut, rrs); Burke, C. N.; Fredrickson, T. N.; DiCapua, A. *J. Natl. Cancer Inst.* 55(1):89-99; 1975.

unodiffusion and fluorescent antibody (FA) tech-ues, and electron microscopy (EM) were used to dy the morphogenesis of Marek's disease virus V) in White Leghorn chickens inoculated intra-cheally at one day of age with skin extract from -infected birds. Skin specimens from the ventral ther tract were processed for EM, homogenized, racted for soluble antigen for ID tests, and then zen for direct staining with FA. Of the three luative systems used, FA and EM were the most sitive methods for the detection of virus. Posi-e results from FA-stained feather follicles cor-ated well with the EM results from adjacent fol-les from the same bird. Positive ID results, ever, were obtained only when EM revealed exten-e lesion development. Virus particles were de-ted in the skin biopsy specimens as early as 12 s after MDV inoculation. Immature naked particles st appeared in the nucleus; later, these particles e enveloped in the cytoplasm and enclosed in oplasmic inclusion bodies. No evidence for con-ued virus replication was seen in the feather fol-les after an initial burst of heavy virus produc-n, which lasted for several weeks. This initial st of virus production was followed by regenera-n of the follicular tissue and loss of inclusion ies containing mature virus. Residual inclusion body material and virion were seen in the stratum corneum of the infected birds; this material, carrying infectious virus, is believed to be released into the environment, and to be the main source of environmental contamination.

3222 PATHOGENIC AND SEROLOGIC STUDIES OF JAPANESE QUAIL INFECTED WITH JM STRAIN OF MAREK'S DISEASE HERPESVIRUS. (Eng.) Mikami, T. (Sapporo Med. Coll., Japan); Onuma, M.; Hayashi, T. T. A.; Narita, M.; Okada, K.; Fujimoto, Y. *J. Natl. Cancer Inst.* 54(3):607-614; 1975.

The pathogenic and serologic effects of the JM strain of Marek's Disease herpesvirus (MDHV) in Japanese quail were investigated. Agar gel-precipitation (AGP) antigen was detected in MDHV-infected birds in both inoculated and contact-exposed birds within 30 days after inoculation. Immunofluorescent antigen for MDHV was found in the cutaneous epidermis and epidermal layers of the follicular epithelium. AGP testing showed that six of 73 quail had antibodies against chicken-positive antigen (CPA). By determing the formation of a continuous line with MD-chicken serum against CPA or quail-positive antigen (QPA), the antigen in quail was found to be MD-specific. Attempts to recover viruses by direct kidney culture failed, but the MD virus was recognized after subpassage of kidney culture cells into embryo fibroblasts. Approximately 87% of the 760 chicken sera had identical reactions to the antigen of infected and/or uninfected fowl; the sera had negative reaction to all four antigens or a positive reaction to CPA and QPA and a negative reaction to CNA and QNA. These results indicate that QPA is specific to MD infection, with most sera reacting specifically with CPA and QPA. The results demonstrate that Japanese quail are susceptible to the JM strain because of serologic and virologic evidence of infection. The specific antigen components could be separated from the nonspecific component of QPA by gel filtration on Sephadex G-150.

3223 POLYPEPTIDES OF MAMMALIAN ONCORNAVIRUSES. II. CHARACTERIZATION OF A MURINE LEUKEMIA VIRUS POLYPEPTIDE (p15) BEARING INTERSPECIES REACTIVITY. (Eng.) Schafer, W. (Max-Planck-Institut fur Virusforschung, Tubingen, West Germany); Hunsmann, G.; Moennig, V.; de Noronha, F.; Bolognesi, D. P.; Green, R. W.; Huper, G. *Virology* 63(1):48-59; 1975.

Polypeptide p15 from Friend leukemia virus was isolated by multiple gel filtration steps in guanidine hydrochloride and characterized by serological tests, double-antibody radioimmunoassay, immunoprecipitation, and polyacrylamide gel electrophoresis. Because of its marked tendency to aggregate, renaturation of the protein was performed in the presence of 0.2% sodium deoxycholate. In Ouchterlony tests, antiserum prepared against p15 (in rabbits) was tested for possible cross reactivity with other virion components. No reaction was obtained with p10, p12, p30, or gp71. The antiserum did react with the homologous polypeptide but only in the presence of 0.2-0.5% sodium deoxycholate. The p15 antiserum

also reacted with the homologous polypeptide in complement fixation. Radioimmunoassays confirmed the observations obtained with immunodiffusions and complement fixation. Precipitation with the p15 serum occurred only with the homologous polypeptide, and competition of the reaction was observed at limiting antibody dilution by the addition of unlabeled p15 but not by the addition of p10, p12, p30, and gp71. Essentially complete cross reactivity was seen in immunodiffusion of p15 antiserum with Friend, Gross, and Rauscher leukemia viruses. Using this test, it did not appear that p15 of Friend leukemia virus contained determinants distinguishable (type specific) from any in Gross leukemia virus, which belongs to a different serotype. When the reactivity of viruses from several species with p15 antiserum was tested in complement fixation, positive reactivity was obtained with murine, rat, hamster, classical feline, and simian oncornaviruses. A marked variation in the specific complement fixation activity was seen in the viruses studied. The reason for this great variation is not clear, but quantitative and qualitative differences may both play a role.

3224 PROPERTIES OF FELINE LEUKEMIA VIRUS. III. ANALYSIS OF THE RNA. (Eng.) Brian, D. A. (Dept. Microbiology and Public Health, Michigan State Univ., East Lansing, Mich. 48824); Thomason, A. R.; Rottman, F. M.; Velicer*, L. F. *J. Virol.* 16(3):535-545; 1975.

The kinetics of virus labeling was used to study the maturation of viral RNA in the Rickard strain of feline leukemia virus. Viral RNA labeled over differing intervals was characterized by gel electrophoresis and velocity sedimentation in sucrose gradients made up in aqueous buffer and 99% dimethyl sulfoxide. Labeled virus was found within 30 min after adding radioactive uridine to the cells, and production of labeled virus reached a maximum at 4-5 hr after pulse labeling. Native RNA from feline leukemia virus resolved into three size classes when analyzed by electrophoresis on 2.0% polyacrylamide-0.5% agarose gels: a 6.2×10^6 to 7.1×10^6 molecular weight (50-60S) class, an 8.7×10^4 molecular weight (approximately 8S) class, and a 2.5×10^4 molecular weight (4-5S) class. From two experiments during which RNA degradation appeared minimal, these made up 57-76%, 2-5%, and 6-12%, respectively, of the total RNA. The 8S RNA in feline leukemia virus has not previously been reported. The 50-60S RNA from virus harvested after four hours of labeling electrophoretically migrated faster and sedimented more slowly in sucrose gradients than did the same RNA species harvested after 20 hr of labeling. This suggests the existence of an intravirion modification of the high-molecular-weight RNA. The large subunits of denatured viral RNA from both 4- and 20-hr labeled-viral RNA electrophoretically migrated with an estimated molecular weight of 3.2×10^6 but sedimented with 28S ribosomal RNA (2.8×10^6 molecular weight) when analyzed by velocity sedimentation through 99% dimethyl sulfoxide.

3225 EXPRESSION OF MURINE LEUKEMIA VIRUS ENVELOPE GYLCOPROTEIN gp69/71 ON MOUSE THYMOCYTES: EVIDENCE FOR TWO STRUCTURAL VARIANTS DISTINGUISHED BY PRESENCE *VS.* ABSENCE OF G_{1X} ANTIGEN. (Eng. Tung, J.-S. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021); Fleissner, E.; Vitetta, E. S.; Boyse, E. A. *J. Exp. Med.* 142(2):518-523; 1975.

Thymocytes of several mouse strains were tested for expression of gp69/71, the envelope glycoprotein of murine leukemia virus, in the plasma membrane by surface iodination, followed by immunoprecipitation and sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis. These strains included two congenic lines differing from their partner stocks with respect to expression of G_{1X} antigen demonstrable in the cytotoxicity assay. The results showed that two structural variants of gp69/71 could be expressed on mouse thymocytes; these were distinguishable by a small difference in mobility in SDS gels. One carried G_{1X} antigen and the other did not. The variants were coded, or their expression was regulated, by different chromosomal loci that were not closely linked. Both could be expressed together on the thymocytes of inbred mice. In the intact thymocyte plasma membrane, the sites of group-specific antigen shared by the two gp69/71 variants, unlike the G_{1X} type specificity carried by only one of them, are probably inaccessible to antibody.

3226 VIROLOGIC AND IMMUNOLOGIC STUDIES OF HUMAN PROSTATIC CARCINOMA. (Eng.) Dmochowski, L. (Univ. Texas System Cancer Center, Houston, Tex.); Maruyama, K.; Ohtsuki, Y.; Seman, G.; Bowen, J. M.; Newton, W. A.; Johnson, D. E. *Cancer Chemother. Rep. (Part 1)* 59(1):17-31; 1975.

Morphologic, tissue culture, immunologic, and biochemical methods were used in an attempt to detect and characterize oncogenic viruses or their subviral components in cells derived from human prostatic carcinoma (PrCa) or benign prostatic hyperplasia (BPH). Electron microscopy was used to characterize the ultrastructural features of normal and neoplastic prostatic tissue. Examination of specimens of prostatic tissue from 34 patients with PrCa, ten patients with BPH, and three patients with bladder tumor (BT) revealed the presence of particles resembling type-C virus in three cases of PrCa and structures resembling budding type-C virus particles in one case of BPH. Fifty human prostatic tissue specimens were set in tissue culture, of which 30 were successfully grown for varying periods of time. Of 20 currently active cultures, nine consisted primarily of epithelial cells. Immunofluorescence and mixed hemadsorption tests of cells derived from benign and malignant prostatic tissue and sera derived from patients with PrCa, BPH, BT, and other types of tumors, and from normal donors revealed that sera from patients with PrCa, BPH, or BT contain antibodies to antigens in cells derived from PrCa, BPH, or BT. Initial biochemical studies did not reveal reverse transcriptase in the tissue culture fluid from a small number of sparsely growing PrCa cultures, nor were specific gene sequences homologous to

ine leukemia virus-Rauscher genomic RNA found preparations of either normal or malignant protic cell DNA. The results of these preliminary dies demonstrate the applicability of the techues employed to the study of the relationship viruses to human PrCa.

7 ROLE OF CELLULAR RNA POLYMERASES IN VIRUS-INDUCED LEUKEMOGENESIS. (Eng.) Babcock, F. (Inst. for Enzyme Res., Univ. of Wisconsin, ison, Wis.); Rich, M. A. *Cancer Res.* 35(8):2078-2; 1975.

stimulation of RNA synthesis in erythropoietic se tissue by Friend murine leukemia virus was died to determine whether this change is assoted with the cellular proliferation caused by the ection, or with the virus replication *per se*. /Ha Swiss mice were inoculated i.p. with a leuogenic dose of the virus. The infection induced enic enlargement and an increase in RNA polymer- activity of spleen nuclei. Actinomycin D µg/kg/day) prevented the development of splenoaly and the elevation of polymerase activity foling infection, but it had only a slight effect on production of virus in spleen tissue. Thus, alteration of RNA synthesis was not a result of us proliferation, but instead may have been a ifestation of leukemic erythropoiesis. Normal thropoiesis, stimulated by erythropoietin adistration (1U,sc, 12 and 24 hr before sacrifice), duced a similar but transient increase in RNA ymerase activity in spleen nuclei. Erythropoietin inistered before, but not after, Friend virus intion resulted in an enhancement of RNA polymerase ivity, as measured nine days after inoculation. results suggest that there is a common target l pool for both erythropoietin and Friend virus, that this pool becomes refractory to the inence of the hormone as a result of the leukemic cess.

8 ALTERATION OF THE SYNCYTIUM-FORMING PROPERTY OF XC CELLS BY PRODUCTIVE MOLONEY KEMIA VIRUS INFECTION. (Eng.) Chan, J. C. D. Anderson Hosp. and Tumor Inst., Houston, Tex. 25); Vera, N.; Allen, P. T.; East, J. L.; sek, J. E.; Bowen, J. M.; Dmochowski, L. *Cancer* . 35(7):1854-1857; 1975.

effect of productive murine leukemia virus LV) infection on the syncytium-forming property XC rat sarcoma cells was studied. MuLV-Moloneyected XC cells, designated XC(M), initially went ough a period of spontaneous syncytium formation. syncytia then disappeared, and XC(M) cells conued to propagage and produce both infectious MuLV MuLV group-specific antigens. However, XC(M) ls became refractory to syncytium formation that induced by Kirsten, Friend, Rauscher, and oney strains of murine oncornaviruses. These a suggest that XC(M) cells lost their syncytiumming ability as a result of productive MuLV infecn.

3229 EVALUATION OF IRRADIATION-PLUS-URETHAN-INDUCED MURINE LEUKEMIA VIRUS "RELEASE" USING A NEW METHOD FOR QUANTITATION OF ONCORNAVIRUSES IN TISSUES. (Eng.) Brown, R. C. (Univ. North Carolina Sch. Med., Chapel Hill); Kostyu, J. A.; Kilgore, A. *Cancer Res.* 35(4):1053-1057; 1975.

A new method for quantitating oncornaviruses in tissues is presented. The method was used to determine whether virus release associated with leukomogenic activity produced by X-irradiation-plus-urethan treatment is related to change in virus quantity. The new method involves the use of a microchamber with the sides situated on rotor radii so as to produce a uniform virus-containing sediment of tissue homogenate-sonicate that is evaluated by electron microscopic examination of thin sections cut perpendicular to the membrane surface. Samples containing as little as 10^5 to 10^6 viruses can be relatively easily counted. Semipurified or purified viruses can also be counted after mixing with a tissue homogenate-bovine serum albumin diluent. RFM/Un mice (4-6 wk old) were given four weekly doses of 170 rads X-irradiation, and C57BL/6J mice received four weekly doses of 200 rads. Both treatments were followed three days later with 1 mg/g urethan ip. The virus quantity was evaluated ten days after the last irradiation. Treated C57BL/6J mice showed numbers of virus no greater than controls (8×10^6 virus/ml in treated mice *versus* 1.1×10^7 virus/ml in controls); similar results were obtained with treated RFM/Un mice (4.0×10^7 in treated *versus* 3.0×10^7 in controls). These results indicate that the leukemogenic activity, shown to be present in such thymus-bone marrow homogenates at this time after irradiation-plus-urethan treatment, is not due to change in quantity of C-type viruses as has been previously proposed.

3230 STUDIES ON VIRUS INDUCTION BY 5-BROMODEOXYURIDINE IN NONPRODUCER MURINE SARCOMA VIRUS-TRANSFORMED 3T3 CELLS. (Eng.) Margalith, M. (St. Louis Univ. Sch. Med., Mo.); Thornton, H.; Narconis, R.; Pinkerton, H.; Green, M. *Virology* 65(1):27-39; 1975.

The properties of the nonproducer KA31 cell line transformed by the Kirsten strain of murine sarcoma virus were studied. Treatment of cells with 5-bromodeoxyuridine (BrdU) induced the synthesis of DNA polymerase-containing particles which band in sucrose gradients at a density of 1.16 and utilize poly(I) $(dC)_{12-18}$, a template-primer specific for RNA-directed DNA polymerase. The induction process was studied by analysis of the culture fluid for polymerase activity; the induced cells were studied for viral proteins by immunofluoresence. Virus particles were studied with the electron microscope. Varying the concentration and the time of exposure to BrdU showed that the maximal level of polymerase activity was induced when cells were treated with 20 µg of BrdU for a 24-hr period, 24 hr after seeding. Under these conditions about 15% of the cells were induced to synthesize viral antigens detected with anti-Moloney murine sarcoma virus rat serum. The level of polymerase activity in the culture fluid and viral antigen in the cells be-

came maximal at three days after BrdU treatment and decreased rapidly. Electron microscopy showed a large increase in the proportion of cells containing incomplete virus particles and in the number of particles per cell at two and three days after BrdU treatment. At three days after treatment, 82% of the cells contained incomplete virus particles within dilated vesicles of the endoplasmic reticulum, as compared to 18% for untreated cultures. KA31 cells, treated with 20 μg/ml BrdU for 24 hr became flat and fibroblastic, as compared to the rounded, transformed morphology of untreated cells. This effect was even more pronounced when cells were maintained and passaged in the presence of 4 μg/ml BrdU. A high level of virus production could be maintained for at least 15 days by continuous maintenance of cells on 4 μg/ml BrdU. It is not clear whether the mechanism involves continuous reinduction of virus or overcoming the normal inhibition of virus multiplication in these cells.

3231 MURINE SARCOMA VIRUS RELATED NUCLEIC ACID SEQUENCES IN A NON-TRANSFORMING VIRUS DERIVED FROM AN INTERSPECIES PSEUDOTYPE SARCOMA VIRUS. (Eng.) Okabe, H. (Flow Lab. Inc., Rockville, Md.); Gilden, R. V.; Hatanaka, M. *Int. J. Cancer* 15(5):849-859; 1975.

The question of whether mouse type-C virus-related sequences detected in the hamster virus GLOH⁻ are derived from Gross passage A virus (GLV) or from Moloney murine sarcoma virus (M-MSV) was investigated. The viruses used included Rauscher leukemia virus (RLV), Harvey-MSV (H-MSV), Akv-1, Graffi-HaLV (G-HaLV), M-MSV(RaLV), and Moloney strain of MuLV, as well as the GLV, M-MSV, and GLOH⁻ viruses. Viral 70S RNA was separated, and single-stranded viral [^{3}H]DNA transcripts complementary to viral RNAs were isolated. [^{3}H]DNA probes were incubated with viral RNA and loaded onto hydroxyapatite (HA) columns. Thermal dissociation (Tm) was also determined. Analysis of transcripts related to M-MSV(RaLV) RNA, revealed a clear relationship to Moloney-related sequences, both in reaction extent and Tm. The GLV transcript showed the same approximate Tm with M-MSV(RaLV) RNA (72.0 C) as with M-MSV RNA (72.6 C). Because of the thermal stability of inter-strain hybrid molecules, and the stability of Moloney virus sequences in a rat-mouse interspecies pseudotype, it is concluded that mouse virus-specific sequences in GLOH⁻ are derived from Moloney virus and not Gross virus.

3232 RELATIONSHIP IN NUCLEIC ACID SEQUENCES BETWEEN MOUSE MAMMARY TUMOR VIRUS VARIANTS. (Eng.) Michalides, R. (Meloy Lab., Inc., Springfield, Va. 22151); Schlom, J. *Proc. Natl. Acad. Sci. USA* 72(11):4635-4639; 1975.

The relationship of the nucleic acid sequences of horizontally transmitted mouse mammary tumor virus (MMTV) variants from four mouse strains to each other and to a vertically transmitted MMTV variant was determined using competition molecular hybridization experiments. Primary cultures of mouse mammary carcinomas were used as a source of both ^{3}H-labeled and unlabeled 60-70S RNA of MMTV. The hybridization experiments revealed that, within the limits of the assay, the RNAs of the MMTVs synthesized in culture by the tumors of the mouse strains RIII, GR, A, and C3H, are identical. A comparison of the genomes of the milk-transmitted MMTV(C3H) and the vertically transmitted MMTV (C3Hf) revealed that these two viruses are approximately 75% similar. No nucleic acid sequence homology was observed between MMTV(C3H) 60-70S RNA and the RNAs of murine leukemia virus, Mason-Pfizer virus, or the bromodeoxyuridine induced type-B guinea pig virus. This assay considers the total genome of the RNA tumor virus and avoids inconclusive results due to the use of incomplete or preferential complementary DNA transcripts. The only disadvantage of the assay is that the hybrid formation excludes some of the added radioactively labeled RNA.

3233 NON-REPETITIVE DNA TRANSCRIPTS IN NUCLEI AND POLYSOMES OF POLYOMA-TRANSFORMED AND NON-TRANSFORMED MOUSE CELLS. (Eng.) Grady, L. J. (Div. Lab. Res., New York State Dept. Health, Albany Campbell, W. P. *Nature* 254(5498)356-358; 1975.

RNA-DNA saturation-hybridization experiments were used to detect the percent of common sequences between non-repetitive DNA and nuclear or polysomal RNA in polyoma-transformed (PY AL/N) or nontransformed (AL/N) cells. Nuclear and cytoplasmic fractions were prepared using 0.05% Triton X-100. Nuclear RNA was obtained and polysomes were purified from the supernatant by discontinuous or linear sucrose density gradient centrifugation. Polysomal RNA was isolated by phenol-chloroform extraction. After further purification, hybridization reactions using the appropriate RNA (12 mg/ml) and labeled, non-repetitive DNA (12 μg/ml) were performed. Time courses of hybridization reactions were plotted and the percent of RNA hybridized to DNA was calculated. In the PY AL/N cells nuclear RNA contained about 30% of the non-repetitive DNA sequences, whereas polysomal RNA contained about 6.4%. In the AL/N cells, the nuclear RNA contained about 20% of the non-repetitive DNA sequences in both subconfluent and confluent growth states. However the polysomes of subconfluent AL/N cells showed a greater percentage of DNA transcripts (about 8.6%) than the polysomes in confluent AL/N cells (5.7%). Both qualitative and quantitative differences appear to exist in the polysomal transcripts in these two growth states.

3234 ELECTROPHORETIC ANALYSIS OF THE STRUCTURAL POLYPEPTIDES OF POLYOMA VIRUS MUTANTS. (Eng.) Frost, E. (Départment de Microbiologie, Centre Hospitalier Universitaire, Université de Sherbrooke, Sherbrooke, Québec, Canada); Bourgaux, P. *Virology* 65(1):286-288; 1975.

The structural polypeptides of wild-type polyoma virus were compared with those of some of its temperature-sensitive (*ts*) mutants using polyacrylamide gel electrophoresis. The study was limited to the early mutant, *ts*-a, two complementing late mutants, *ts*-10 and *ts*-1260, the noncomplementing *ts*-3, and

the TSP-1 isolate of the wild type. For virus production, secondary cultures of whole mouse embryos infected at low multiplicity (0.5 plaque forming U/cell) were incubated for two weeks at 33 C. The virus was harvested using receptor-destroying enzyme, purified, and labeled with either ^{131}I or ^{125}I using chloramine-T. Labeled virus was separated from unreacted iodine by velocity centrifugation in a sucrose solution. The ^{131}I-labeled mutants were mixed with ^{125}I-labeled wild-type virus prior to dissociation and electrophoretic separation. No differences were found in the electrophoretic mobilities of the polypeptides from wild-type polyoma virus; *ts*-a, *ts*-3, and *ts*-1260. Mutant *ts*-10 contained two polypeptides migrating slightly slower than their wild-type counterparts. Since there is no evidence to suspect that the genome of *ts*-10 contains more than one mutation, these data provide evidence that these two structural polypeptides are either coded for or dependent on the same viral gene and possibly are cleavage products from a precursor molecule.

3235 FORMATION OF NUCLEOPROTEIN COMPLEXES BETWEEN POLYOMA EMPTY CAPSIDS AND DNA. (Eng.) Aposhian, H. V. (Univ. Maryland Sch. Med., Baltimore); Theyer, R. E.; Qasba, P. K. *J. Virol.* 15(3):645-653; 1975.

Binding studies were made with polyoma virions or empty capsids, and polyoma DNA. Virions and capsids were produced by infecting primary mouse embryo cells (1 plaque-forming unit/cell). To the medium was added 10 μCi of L-[^{3}H]tryptophan (3 Ci/mM) 18 hr after infection, or [^{3}H]arginine (20.6 Ci/mM) 20 hr after infection. Labeled DNA was produced by adding [^{14}C]thymidine (56 mCi/mM) or [^{3}H]-thymidine (20 Ci/mM) to baby mouse kidney cells 18 hr after polyoma infection. The DNA was extracted 48 hr after infection. For assay of complex formation, 0.61 g polyoma [^{3}H]DNA and designated amounts of capsid protein or virions were incubated in a standard reaction mixture for 60 min at 37 C and centrifuged in a sucrose gradient. Incubation of unlabeled empty capsids with the DNA caused a change in the sedimentation pattern of DNA alone; instead of the radioactivity remaining at the top of the gradient, it formed a number of new peaks. Addition of 7-10S capsomeres instead of whole empty capsids resulted in the DNA remaining at the top; their addition to mixtures already containing whole capsids did not affect formation of capsid-DNA complexes. Addition of virions to the reaction mixture did not affect the normal sedimetation of the DNA, and their addition to mixtures already containing empty capsids did not affect the multipeaked profile normally obtained from this mixture. DNA and empty capsids formed two major peaks at 144S and 240S. The 140S product contained polypeptides normally found in the capsids. It contained the least amount of protein relative to DNA, while a third 370S peak contained four times as much. Electron microscopy of the reaction mixture before sedimentation showed capsid-DNA complexes with 1, 2, 3, or 4 capsids/DNA molecule. The 140S, 240S, and 320S complexes contained 1, 2, and 3 capsids/DNA molecule, respectively. NaCl (0.50 M) prevented complex formation. Many sedimentation peaks were inhibited by pretreatment of the DNA with DNase, or by treating the capsids with pronase. The demonstration that empty polyoma capsids form complexes with DNA, while whole virions do not, suggests that the empty capsids contain some site(s) that have an affinity for DNA. The author suggests that the site(s) may be attached to or part of the inner surface of the empty capsids or, alternatively, at a possible point of incompleteness of some of the empty capsids.

3236 A COMPARATIVE STUDY OF BK AND POLYOMA VIRUSES. (Eng.) Seehafer, J. (Dept. Biochemistry, Univ. Alberta, Edmonton, Alberta, Canada); Salmi, A.; Scraba, D. G.; Colter, J. S. *Virology* 66(1):192-205; 1975.

The molecular anatomies of BK and polyoma (Py) viruses were compared by hemagglutination and hemagglutination inhibition tests, sodium dodecyl sulfate-polyacrylamide gel electrophoresis, centrifugal analysis of viral DNA in alkaline sucrose density gradients, and electron microscopy. The viruses were purified by a procedure involving precipitation of the virus from crude lysates with methanol, sequential treatment of the resuspended methanol precipitate with DNase and RNase, clarification of the suspension by chloroform extraction, sedimentation of the virus through 20% sucrose solution, and equilibrium centrifugation in CsCl density gradient. The capsids of both were found to be composed of 72 capsomeres arranged in a T = 7d icosahedral lattice. Analysis of the DNAs of the two viruses suggested that the full-length DNA of BK virus may be slightly smaller than that of Py virus. The two virions contained the same number of structural polypeptides, but the molecular mass of BK-VP1 was about 4,000 daltons less, and those of BK-VP2 and 3 about 4,000 daltons more than those of the corresponding Py polypeptides. The observation that the major capsid polypeptide, BK-VP1, was smaller than Py-VP1, was compatible with the observed difference in the diameters of the two virions (BK = 405 ± 10 Å; Py = 430 ± 15 Å). The two viruses differed sharply in the relative efficiencies with which they hemagglutinated guinea pig and human RBC. BK virus, unlike Py virus, replicated only in certain human or monkey cells; human fetal kidney cells were found to be the most satisfactory for the propagation of this agent. On the whole, the results demonstrate a striking similarity in the molecular anatomies of BK and Py viruses.

3237 RELATIONSHIP BETWEEN A-TYPE AND C-TYPE PARTICLES IN CELLS INFECTED BY ROUS SARCOMA VIRUS. (Eng.) de Giuli, C. (Rockefeller Univ., New York, N.Y. 10021); Hanafusa*, H.; Kawai, S.; Dales, S.; Chen, J. H.; Hsu, K. C. *Proc. Natl. Acad. Sci. USA* 72(9):3706-3710; 1975.

The antigenic relationship between Rous sarcoma virus (RSV) and cytoplasmic A-type particles occasionally found in RSV-infected chicken embryo cells (type C/E) and the circumstances surrounding

the formation of such particles were investigated using various RSV strains (Schmidt-Ruppin subgroup A and D, and a temperature sensitive mutant ts68) and several Rous-associated strains (RAV). To detect A particles, cells were washed repeatedly, made permeable by a two-minute exposure to .005% Nonident P40 (NP40), centrifuged (800 x *g* for ten minutes), and resuspended in Eagle's MEM medium. For 30 min cells were incubated at 37 C with monospecific antiserum against RAV-2 proteins p27, p19, and p15. Cells were then centrifuged and resuspended twice. Sections were prepared and stained. Because so few sections revealed A particles, the statistical frequency of A particle occurrence was determined by treating cells at 0 C with 0.25 or 0.5% NP40 to partially solubilize organelles, and centrifugation at 1200 x *g* for 30 min; this produced particle-enrichment. Results demonstrated that A particles contain components immunologically related to the internal proteins of C-type virus particles. RSV-infected cultures contained A particles more consistantly than RAV-infected cultures. Normal cells contained no A particles. Particles were present in 5-30% of infected cell profiles, suggesting that they are not an obligatory precursor to C particles, because then a higher percentage would be expected. Cell cultures infected with serial dilutions of RAV-2^4 and passage every three days were examined for gross cytopathological changes and the frequency of A particle appearance; the higher the initial concentration of virus, the sooner both cytopathological change and A particles appeared. It is suggested that A particles are formed as a product of C-type virus infection and develop in cells undergoing cytopathological degeneration.

3238 EFFECT OF ONCOGENIC VIRUS ON MUSCLE DIFFERENTIATION. (Eng.) Holtzer, H. (Sch. Medicine, Univ. Pennsylvania, Philadelphia, Pa. 19174); Biehl, J.; Yeoh, G.; Meganathan, R.; Kaji, A. *Proc. Natl. Acad. Sci. USA* 72(10):4051-4055; 1975.

The question of whether some events that control differentiation can modulate the course of viral-induced transformation was investigated in breast muscle cells from leukosis-free ten-day chick embryos. Chick muscle cultures infected with the Prague strain of Rous sarcoma virus formed myotubes, but these myotubes vacuolated; by day six, most had degenerated, leaving only large numbers of transformed mononucleated, replicating cells. Muscle cultures infected with a temperature-sensitive mutant (ts) at permissive temperatures (36 C) behaved as cells infected with wild-type Rous sarcoma virus. Temperature-sensitive infected cells reared for eight days at nonpermissive temperature (41 C) formed contracting myotubes, plus large numbers of fibroblastic cells. If these cultures were incubated at the permissive temperature, the myotubes vacuolated and degenerated within 72 hr, whereas the mononucleated cells became transformed. If replicating ts-transformed cells after eight days at permissive temperature were shifted to nonpermissive temperature, many cells fused and formed contracting, post-mitotic myotubes within 72 hr. Creatine kinase (ATP:creatine *N*-phosphotransferase) levels paralleled the formation and degeneration of myotubes during these temperature shifts. If the viral transforming gene was expressed in the post-mitotic myotubes, it was lethal; it was not lethal if expressed in replicating precursor myogenic cells. The data contribute to the following points regarding basic controls in the neoplastic cell. The viral gene expression at permissive temperature blocks further myogenesis depending on the position of the cells in the myogenic program. The virus does not cancel the replicating, transformed myogenic cells' commitment or position in, the myogenic lineage. When the transforming action of the virus is suppressed, the normal myogenic program resumes.

3239 INFECTIOUS DNA CODING FOR A TEMPERATURE-SENSITIVE DNA POLYMERASE OF THE COORDINATE *LA*335 MUTANT OF ROUS SARCOMA VIRUS (RSV). (Eng.) Hillova, J. (Inst. Cancerology and Immunogenetics, Villejuif, France); Mariage, R.; Hill, M. *Virology* 67(1):292-296; 1975.

The DNA from chick embryo fibroblasts (CEF) transformed by Prague strain Rous sarcoma virus, subgroup C (PR-C) or a Rous sarcoma virus (RSV) temperature-sensitive (ts) mutant (*LA*335) was used in transfection experiments to determine if the DNA polymerase of the recovered virus is specified by the infectious DNA of the recipient cell in this assay. Most transfection assays were carried out using a DEAE-dextran pretreatment, but in one experiment the technique using coprecipitation of the DNA with calcium phosphate was employed. The DNA extracted from *LA*335-transformed CEF gave rise in the transfection experiments to transforming viruses. These viruses exhibited a ts lesion in early functions similar to that characteristic of the *LA*335 mutant. One of the recovered viruses was further examined for a DNA polymerase activity at the permissive and nonpermissive temperatures and was found to carry an enzyme with a thermosensitivity similar to that of the DNA polymerase of *LA*335. It is concluded that the infectious viral DNA extracted from RSV-transformed cells carries the genetic information for the DNA polymerase specific for the parent virus. This information is transferred to the progeny virus upon transfection to permissive cells.

3240 RNA OF REPLICATION-DEFECTIVE STRAINS OF ROUS SARCOMA VIRUS. (Eng.) Duesberg, P. H. (Dep. Mol. Biol. Virus Lab., Univ. California, Berkeley); Kawai, S.; Wang, L.-H.; Vogt, P. K. Murphy, H. M.; Hanafusa, H. *Proc. Natl. Acad. Sci. USA* 72(4):1569-1573; 1975.

The RNA of a replication-defective (*rd*) mutant [isolated from nondefective (*nd*) Schmidt-Ruppin Rous sarcoma virus of subgroup A (SR-A) and designated SR-N8] was compared to the RNAs of SR-A, transformation-defective (*td*) SR-A, and to *rd* Bryan Rous sarcoma virus, RSV(-). SR-N8-transformed chick embryo fibroblasts were infected with *td* SR-A to form SR-N8 pseudotypes. The RNAs of all species were subjected to electrophoresis in aqueous and formamide polyacrylamide gel. The 30-40S RNA of

SR-N8 migrated faster than the 30-40S RNA from SR-A or RSV(-) but did show some asymmetry when compared to standards. The 30-40S RNA of RSV(-) had the same mobility as RAV-2 RNA standard. *Td* SR-A had a higher mobility than SR-A, but lower than that of RAV-2. The difference in molecular mass between the 30S and 40S RNAs of SR-A and SR-N8 was 0.75 x 10^6 daltons. Using fingerprint analysis, a homologous oligonucleotide spot was found in the pattern of SR-A for every large spot of SR-N8 RNA. The *td* SR-A contained all but two oligonucleotide spots found in SR-A. Comparing the fingerprint patterns of SR-A, SR-N8 and *td* SR-A suggests that the deletions affecting transforming ability and those affecting a replicative function involve different regions of the viral RNA. Eleven of 13 large RNase T_1 resistant oligonucleotides of SR-N8 have a counterpart in SR-A. The complexity of SR-A RNA was calculated at 1.17 x 10^4 nucleotides and SR-N8 at 0.93 x 10^4 nucleotides; the average nucleotide of the two RNAs had a molecular mass of 323 daltons. It is concluded that RNA of SR-N8 is a deletion of SR-A.

3241 SIZE AND DISTRIBUTION OF SV 40 DNA SEQUENCES COVALENTLY LINKED WITH THE DNA OF PERMISSIVE MAMMALIAN CELLS. (Eng.) Kuhn, C. (Institut für Virusforschung, Deutshces Krebsforschungszentrum Heidelberg, Germany); Waldeck, W.; Sauer, G. *Z. Krebsforsch.* 83(1):65-79; 1975.

Linear duplex DNA molecules consisting of covalently linked simian virus 40 (SV40)-host DNA sequences were isolated from SV40-infected CV-1 cells and characterized. CV-1 cell cultures were infected at a low multiplicity (0.5 plaque forming units/cell), labeled with [^{3}H]thymidine (20 µCi/ml), and the DNA was selectively extracted. The DNA obtained from the NaCl-dodecyl-SO_4-supernatant was subjected to dye-buoyant-density CsCl-ethidium bromide equilibrium centrifugation; the light band containing relaxed circular and linear duplex DNA structures was used for further investigation of the viral-host DNA sequences. These molecules were isolated and purified by two successive cycles of DNA-DNA hybridization and elution steps using first CV-1 cell and then SV40-DNA·immobilized on filters. In studies of the reassociation kinetics of this material, only part of the isolated DNA sequences (40%) was able to reassociate rapidly, while most of the DNA sequences reassociated slowly. This suggests the participation of various unique DNA sequences in formation of such viral-host DNA molecules. Treatment of the reassociated viral-host DNA sequences with single strand-specific S_1 nuclease confirmed that unique host DNA sequences were always present near the viral DNA. Experiments with fragmented DNA molecules revealed an intimate association of repetitive CV-1 DNA with the SV40 DNA; the reiterated host DNA was confined to within the range of 800 bases from the viral sequences. The results suggest that most of the SV40 DNA sequences are probably integrated as fragments of subgenomic length. These results also suggest an arrangement of interspersed small repetitive sequences alternating with longer unique sequences within the CV-1 cell DNA. The author suggests that the presence of unique host DNA sequences within the purified viral-host DNA may reflect a higher degree of organization of the DNA of higher organisms.

3242 INTERACTION OF PARTIALLY PURIFIED SIMIAN VIRUS 40 T ANTIGEN WITH CIRCULAR VIRAL DNA MOLECULES. (Eng.) Jessel, D. (Sidney Farber Cancer Cent., Boston, Mass.); Hudson, J.; Landau, T.; Tenen, D.; Livingston, D. M. *Proc. Natl. Acad. Sci. USA* 72(5):1960-1964, 1975.

A DNA binding assay for identifying a DNA binding activity in T-antigen-containing fractions is presented. T-antigen was extracted and purified from simian virus 80 (SV80), a line of SV40-transformed human cells. The small-plaque strain of SV40 (SVS) was propagated in primary African green monkey kidney cells. SV40 DNA I was isolated from infected Vero cells, and other viral DNA molecules were isolated and purified. During the DNA binding assay, nitrocellulose filters were used to filter the basic reaction mixture of 0.01 M Tris x HCl (pH 7.4), 0.1 mM manganese acetate, 0.1 mM dithiothreitol, 3% dimethylsulfoxide, 10 µg/ml bovine serumalbumin, SV40 [^{3}H]DNA I, and T protein. Two 0.10 ml aliquots were individually filtered. A complement fixation test for T-antigen was carried out. T-antigen cotracked with DNA binding activity on three types of columns: DEAE-cellulose, agarose A-1.5m, and phosphocellulose. Heat inactivation kinetics of DNA binding activity and T-antigen immunoreactivity paralleled each other. The T-antigen fraction did not recognize DNA sequences unique to SV40 DNA. T-antigen may be the DNA binding protein detected, but it is possible that it is a non-T protein that cochromatographs and has the same heat lability. It is likely that T-antigen is the DNA binding protein observed; a filter binding assay of [^{3}H]DNA may more efficiently measure quantitative aspects of this protein.

3243 *IN VITRO* TRANSFORMATION OF RAT AND MOUSE CELLS BY DNA FROM SIMIAN VIRUS 40. *(Eng.)* Abrahams, P. J. (Lab. Physiological Chemistry, Univ. Leiden, Wassenaarseweg 72, Leiden, Netherlands); van der Eb, A. J. *J. Virol.* 16(1):206-209; 1975.

The transformation of rat kidney cells and mouse 3T3 cells by simian virus 40 (SV40) DNA was investigated employing the calcium technique. SV40 clone 307 L was grown in BSC-1 cells; viral DNA was extracted and banded in CsCl. Only the closed-circular DNA present in the dense band was used in infection of kidney cells. The cells were infected by adding 0.02-8.00 µg viral DNA, 5.0 µg salmon sperm DNA, and 125 mM $CaCl_2$ at pH 7.05 to each dish. Several colonies were isolated and established as cell lines; all lines tested were found to contain SV40-specific T antigen in 95-100% of the cells. The dose response curve for transformation of primary rat kidney cells with SV40 DNA was not linear, and indicated a highest transformation efficiency at low viral DNA concentrations. A clone of 3T3 cells was also transformed by SV40 DNA. Although all cell lines tested contained SV40-specific T antigen in 95-100% of the cells, the 3T3 cells were

found more difficult to handle and maintain. It was thus demonstrated that a reproducible transformation of cells *in vitro* with SV40 DNA could be obtained *via* the calcium technique. In addition, preliminary experiments indicate that transformation of rat kidney cells with linear SV40 molecules and specific DNA fragments is also possible.

3244 REGULATION MECHANISM OF SIMIAN VIRUS 40 LATE GENE EXPRESSION IN PRIMARY MOUSE KIDNEY CELLS AND SIMIAN VIRUS 40 TRANSFORMED 3T3 CELLS. (Eng.) Graessmann, M. (Institut fur Molekularbiologie und Biochemie der Freien Universitaet Berlin, Berlin 33, Arnimallee 22, Germany); Graessmann, A. *Virology* 65(2):591-594; 1975.

Primary and continuous lines of mouse cells are nonpermissive for simian virus 40 (SV40); these cells, infected by the conventional virus absorption method, promote expression of the early but not of the late viral genes. To determine whether a specific factor prevents the expression of the late virus genes, SV40 V-antigen synthesis was studied in primary mouse kidney cells and SV40-transformed BALB/c 3T3 cells (SV-T2) infected with SV40-DNA component I by the microinjection technique. Induction of V antigen was observed in a large number of mouse kidney and SV-T2 cells, and the proportion of cells synthesizing antigen was correlated with the quantity of DNA molecules injected. The results support the hypothesis that restriction of the late SV40 gene expression is directed by a cellular factor(s) in these cells. They do not support the hypothesis that failure of late SV40 gene functions is due to a lack of a factor required for late gene expression.

3245 ACTION OF S_1 NUCLEASE ON NICKED CIRCULAR SIMIAN VIRUS 40 DNA. (Eng.) Chowdhury, K. (Institut für Virusforschung, Deutsches Krebsforschungzentrum, 69 Heidelberg); Gruss, P.; Waldeck, W.; Sauer, G. *Biochem. Biophys. Res. Commun.* 64(2): 709-716; 1975.

Simian virus 40 (SV40) DNA form II, generated either by radiation damage or by DNase and containing on the average more than one single strand nick/molecule, was treated with S_1 nuclease to test the hypothesis that S_1 might be a reagent to extend single strand nicks into double strand breaks. The reactions were carried out at 37 C for 30 min. Under these conditions 2 µl of S_1 nuclease hydrolyzed denatured ^{3}H-labeled SV40 DNA form II (2 µg) to the extent that 95% of the radioactivity was no longer in acid precipitable form; native SV40 DNA form II was not rendered acid soluble. The reaction products were analyzed by both alkaline sucrose velocity sedimentation and by agarose gel electrophoresis. Linear duplex molecules of unit length (form III) were generated at the enzyme concentration sufficient to achieve 95% hydrolysis of at least 100 times the amount of single-stranded DNA. This reaction was dependent on the concentration of the S_1 nuclease. Over a wide range, comprising a tenfold increase of enzyme concentration, form III was generated exclusively, and no smaller DNA duplex was produced. If, under these conditions preexisting single-strand nicks were continued by the enzyme into double strand breaks, then a steady decrease of form III with concomitantly increasing amounts o smaller products should be observed. It is concluded, therefore, that S_1 nuclease introduces only one double strand break per molecule, despite the presence of several single strand nicks.

3246 TRANSCRIPTION OF SIMIAN VIRUS 40 DNA BY *ESCHERICHIA COLI* RNA POLYMERASE: SYNTHESIS OF A DNA-RNA HYBRID AND DISCRETE RNAs UNDER RESTRICTIVE TRANSCRIPTION CONDITIONS. (Eng.) Lebowit P. (Yale Univ. Sch. Med., New Haven, Conn.); Bloodgood, R. *J. Mol. Biol.* 94(2):183-201; 1975.

Restrictive polymerization conditions were applied to the simian virus 40 (SV40) DNA transcription system in an attempt to obtain specific RNA products. Transcriptions were carried out for 30 min at 37 C in reaction volumes of 125 µl containing 0.18 M KCl, 0.033 M Tris-HCl, 6 mM mercaptoethanol, 3.3 mM $MgCl_2$ 5.5 µM-0.165 mM ATP, CTP, GTP, and UTP, 4 µg SV40 DNA I, and 10 µg *Escherichia coli* RNA polymerase. For internal labeling, one substrate with ^{32}P in the alpha position was used. Synthesis of RNA labeled in the 5' terminal positions were performed with either [γ-^{32}P]ATP or [γ-^{32}P]GTP as substrate. Substrate incorporation into RNA was calculated from the amounts of radioactivity in the RNA, and substrate peaks were eluted from Sephadex G100 columns. Column fractions containing RNA were pooled, and the RNA was precipitated at 20 C in the presence of 200 µg phenol-treated *E. coli* carrier transfer RNA, 2% potassium acetate and 66% ethanol. Complementary RNA was analyzed by neutral sucrose velocity sedimentation and acrylamide gel electrophoresis, which revealed the presence of a 21S template DNA-RNA hybrid molecule and a large number of discrete RNAs of 5-11S. The finding that the labeled RNA in the 21S hybrid can be chased from this molecule by the addition of cold substrates to the transcription reaction indicates that the DNA-RNA hybrid serves as an intermediate in transcription of SV40 DNA *in vitro*. It is concluded that the discrete RNAs are transcribed from all areas of the genome, are initiated at specific DNA loci, and probably arise as a result of enhanced specificity at the level of chain determination.

3247 ISOLATION AND PARTIAL CHARACTERIZATION OF A NUCLEAR RNA POLYMERASE -- SV40 DNA COMPLEX. (Eng.) Gariglio, P. (Laboratoire de Génétique, Faculté des Sciences, Université libre de Bruxelles, rue des Chevaux, 67 -- B 1640 Rhode St Genèse, Belgium); Mousset, S. *FEBS Lett.* 56(1): 149-155; 1975.

Permissive African Green Monkey Kidney cells (CV1) were infected with simian virus 40 (SV40) at high multiplicity (30-50 plaque-forming U/cell), and the SV40 DNA-RNA polymerase complex was described. The cellular nuclei were isolated, lysed with sarkosyl (0.5%) and the chromatin separated by centrifugation (30,000 X *g*, 30 min, 2 C). The super-

natant fraction was assayed for RNA polymerase activity. Control cells were treated similarly, but without SV40 infection. Sarkosyl supernatants displayed an active endogenous RNA synthesis as determined by the [^{3}H]uridine monophosphate ([^{3}H]UMP) incorporated into trichloroacetic acid-precipitable material. Transcription was not observed in similar extracts from control cells, indicating that viral infection was responsible for this activity. The sarkosyl supernatant prepared 42 hr after infection was more active (7,101 cpm [^{3}H]UMP incorporated) than that obtained 24 hr after infection (2,207 cpm), suggesting that the number of templates active in transcription increased with the number of viral copies. The activity of sarkosyl extracts was reduced to that of the control cells with the addition of α-amanitin. [^{3}H]UMP incorporation dropped from 2,420 cpm at 4×10^{-3} μg/ml to 161 cpm at 4×10^{1} μg/ml α-amanitin. This suggests that the RNA synthesis was performed by polymerase B or II (the enzymes responsible for SV40 transcription in the nuclei of infected monkey cells). In addition, arifamycin derivative, AF/103, had no effect on the transcription activity of the complex even at very high concentrations (200 μg/ml). Hybridization experiments proved that this complex was virus-specific. It is concluded that the nucleoprotein complex present in sarkosyl supernatants exhibits the properites of an active virus-specific transcription complex for the following reasons: (a) It was found only after infection. (b) Its polymerase molecules initiated RNA synthesis *in vivo* and were highly sensitive to α-amanitin inhibition. (c) The RNA product contained exclusively SV40 sequences.

3248 NUCLEASE DIGESTION OF THE DNA•PROTEIN COMPLEX FROM SIMIAN VIRUS 40 VIRIONS. (Eng.) McCann, P. P. (Natl. Inst. of Arthritis, Metabolism, and Digestive Diseases, Natl. Inst. Health, Bethesda, Md.); Martin, R. G. *Biochim. Biophys. Acta* 395(3): 280-283; 1975.

Previously published reports that a protein is bound at a unique site on the simian virus 40 (SV40) genome were investigated by digesting (a) a DNA-protein complex obtained by alkaline degradation of purified SV40, (b) the purified SV40 DNA, and (c) the DNA-protein complex covalently bound by formaldehyde treatment. Incubation of the DNA-protein complex with staphylococcal nuclease (5 μg/ml) resulted in digestion of essentially all the DNA within one hour. Purified SV40 (protein-free) DNA was also essentially digested within one hour (more than 99.65%) and was not distinguishable from the digestion of the DNA-protein complex. When the formaldehyde-treated DNA-protein complex was subjected to nuclease digestion, a specific and very reproducible difference was seen; 1% of the DNA always remained undigested even after 24 hr of incubation. A control experiment proved that the formaldehyde treatment did not result in interchain cross-linking of the DNA because the SV40 (protein-free) DNA treated with formaldehyde under the same conditions was fully denaturable by the nuclease. Thus, the 1% undigested DNA did represent the area of the tion of the formaldehyde-treated complex, the remaining fragment was treated with Pronase (0.5 mg/ml) to remove the protein; the DNA was sedimented on a neutral sucrose gradient along with a marker of calf thymus DNA of 105 nucleotide pairs. The marker calf thymus DNA sedimented 5.0S, while the nuclease-resistant piece of DNA sedimented at 3.1S. The molecular weight of the protected piece of DNA was estimated at 15,000, which would represent 25 nucleotide base pairs. This figure is within the range of the one derived from the nuclease digestion of the complex, which was 1% of the total SV40 DNA protected or 60 nucleotide base pairs. These results are consistent with the previously published statements that the DNA-protein complex consists of a protein (possibly that specified by the D cistron of SV40) associated with the genome at a unique site.

3249 ENHANCEMENT OF SV40 TRANSFORMATION BY TREATMENT OF C3H2K CELLS WITH UV LIGHT AND CAFFEINE. I. COMBINED EFFECT OF UV LIGHT AND CAFFEINE. (Eng.) Ide, T. (Inst. Medical Science, Univ. Tokyo, Shirokanedai 4-6-1, Minatoku, Tokyo, Japan); Anzai, K.; Andoh, T. *Virology* 66(2):568-578; 1975.

The effect of caffeine (0-4 mM) in conjunction with UV (0-150 ergs/mm^2/sec) or x-ray (0-500 R/min) irradiation on the transformation frequency produced by simian virus 40 (SV40) was studied in the C3H2K mouse kidney cell line. In some experiments, the cultures were also treated with dibutyryl cyclic-AMP (0.1 mM) or theophylline (0.5 mM). The cell cultures were irradiated, infected with virus suspension, and incubated for four days with caffeine. Plating efficiency and transformation frequency were then determined. In the absence of virus, no foci of transformed cells were seen in cultures treated with UV, x-rays, and/or caffeine. Plating efficiencies of control and SV40-infected cells were essentially the same. UV, x-rays, and caffeine decreased the plating efficiency; increasing dosages of caffeine resulted in increasing potentiation of the effect of irradiation. UV, x-rays, and caffeine enhanced the frequency of SV40-induced transformation. Irradiation of cells with increasing doses of UV just before infection resulted in a 2-fold enhancement of the transformation frequency up to a dose of 90 ergs/mm^2 and a 3.3-fold increase at 150 ergs/mm^2. The addition of 1 mM caffeine to nonirradiated cells also enhanced the transformation frequency by 2-fold. When the cultures were irradiated and treated with 1 mM caffeine, the enhancement was about 4-fold up to a UV dose of 90 ergs/mm^2 and 5.9-fold at 150 ergs/mm^2. When 0.1-4 mM caffeine was added, the absolute number of transformations increased, resulting in an enhancement ratio of 1.3-6.8. After the addition of similar doses of caffeine to UV-irradiated cultures (75 ergs/mm^2), the enhancement of transformation frequency ranged from 2.0-13.3. The transformation frequency was not appreciably affected by the addition of dibutyryl cyclic-AMP or theophylline. The results suggest that irradiation and caffeine had a greater than additive effect on transformation, and that they modified and stimulated different sites in the over-all transformation process. The intimate

involvement of DNA repair processes in oncogenic transformation is strongly suggested.

3250 PROPERTIES OF PROSTATIC CULTURES TRANSFORMED BY SV40. (Eng.) Paulson, D. F. (Duke Univ. Medical Center, Durham, N. C. 27710); Bonar, R. A.; Sharief, Y.; Vergara, J. R.; Reich, C.; Shah, K. V. *Cancer Chemother. Rep. (Part 1)* 59(1):51-55; 1975.

The characteristics of Syrian golden hamster prostatic tissue established in explant culture and infected with a 10^6-cell tissue culture infectious dose (50% effective) of simian virus 40 (SV40) were studied. After *in vitro* transformation, the cells were produced in quantity, and 60 x 10^6 cells were injected sc into two adult male Syrian golden hamsters 24 hr after 400 rads of whole-body radiation. After 60-90 days, one small palpable tumor developed. This tumor could be serially transplanted in adult male animals without immunosuppression. The tumor cells were established in tissue culture, and the cells were returned to adult animals without immunosuppression where they rapidly produced fast-growing tumors. The solid tumors were composed of sheets of pleomorphic polygonal cells with large nuclei and many nucleoli; they resembled undifferentiated human prostatic carcinoma. *In vitro*, the cultures contained small, rapidly growing cells with a population doubling time of about 1.3 days. The cells carried the SV40-specific antigen. The modal chromosome number was 66-68 with a distribution of 47-120. Cells exposed to 2-bromo-5'-deoxyuridine (1 x 10^4 M for two days) in culture did not release particles with RNA-dependent DNA polymerase activity. Endocrine sensitivity *in vivo* and *in vitro* is undetermined to date.

3251 TEMPERATURE-SENSITIVE MUTANTS OF SIMIAN VIRUS 40 SELECTED BY TRANSFORMING ABILITY. *(Eng.)* Yamaguchi, N. (Inst. Med. Sci., Univ. Tokyo, Japan); Kuchino, T. *J. Virol.* 15(6):1297-1301; 1975.

Eight temperature-sensitive (TS) mutants of simian virus 40 (SV40) were isolated by UV irradiation or hydroxylamine treatment of wild-type (WT) parental SV40 virus propagated in cultures of African green monkey (AGMK) cells or GC7 cells, a clonal AGMK cell line. The eight mutants were able to transform nonpermissive rat cells at 32.5 C but not at 38.5 C, and were also temperature sensitive for replication in permissive AGMK or GC7 cells. In rat cells, WT virus and a control ts mutant with unimpaired transforming ability formed 1.2- to 2.2-fold more foci at 38.5 C than at 32.5 C, whereas the eight transformation-defective mutants formed 9- to 125-fold fewer foci at 38.5 than at 32.5 C. Although these results indicated that a viral function required for formation of dense foci in rat cells is also necessary for SV40 replication in monkey cells, the temperature sensitivity of the ts gene function was expressed differently in transformation and viral replication. For example, the efficiency of plaque formation of two ts mutants in rat cells and permissive GC7 cells was equal at both 38.5 and 32.5 C, but the efficiency of transformation was 30-fold higher at 32.5 than at 38.5 C. Even in this case, the same ts gene product may be required for transformation and for viral replication since the plaque-forming capacity of one of these two mutants was 50% less than that of WT viru at 38.5 C, and the mutant produced a 1000-fold lowe virus yield at 40.5 than at 35 C at a low multiplicity of infection. Five of the ts mutants were classified into one complementation group that may correspond to Tegtmeyer's group A. No mutant incapable of transforming rat cells at either temperature was isolated.

3252 MURINE ONCORNAVIRUS ACTIVATION IN THE PANCREAS DURING INFECTION WITH VENEZUELAN EQUINE ENCEPHALITIS VIRUS. (Eng.) Harrison, A. K. (Center for Disease Control, Public Health Service, Atlanta, Ga. 30333); Murphy, F. A. *J. Natl. Cancer Inst.* 55(4):917-923; 1975.

Electron microscopic studies of the pancreases of 3-wk-old ICR Swiss mice infected with Venezuelan equine encephalitis virus were undertaken. Fifteen mice were inoculated ip with 10^4 plaque-forming units of virus grown in BHK-21 cells and killed six days post inoculation (at which time they were moribund). Significantly more type-C particles were found in these animals than were found in uninfected controls. This phenomenon was apparentl possible because of the microanatomy of the pancrea in which interstitial spaces allowed accumulation of virus particles.

3253 SELECTIVE BLOCKAGE OF INITIATION OF HOST PROTEIN SYNTHESIS IN RNA-VIRUS-INFECTED CELLS. (Eng.) Nuss, D. L. (Roche Inst. Mol. Biol. Nutley, N. J.); Oppermann, H.; Koch, G. *Proc. Natl Acad. Sci. USA* 72(4):1258-1262; 1975.

Hypertonic mediums were used to study the process of virus-directed suppression of protein synthesis in RNA virus-infected cells. Adsorption of poliovirus type 1 (Mahoney) and VSV (Indiana) was allowe to occur at room temperature for 20 min with HeLa cells. Cells were then transferred to hypertonic medium for 15 min and then pulse-labeled with [^{3}H]-leucine and [^{35}S]methionine at NaCl concentrations of 210, 230 and 250 mM. The NaCl inhibition increased to 80, 65 and 40%, resp., by three hr after infection. The increase in resistance at two salt concentrations (210 and 230 mM) was related to infection by reovirus. Uninfected BHK cells showed more resistance to NaCl inhibition than HeLa cells. In poliovirus-infected HeLa cells the rate of protein synthesis rapidly declined by 75% by two hr post infection. The kinetics of viral RNA synthesi coincides with the increase in protein synthesis resistant to inhibition by excess NaCl. This temporal relationship suggests that the two events were directly linked. There was also a selective blocking of the host peptide inactivation after exposing virus infected cells to hypertonic media, indicating that virus messenger RNA translation

s more efficient than in host messenger RNA. Cl apparently lowers the rate of initiation by tering the affinity between ribosomes and messen- r RNA.

54 COVALENTLY LINKED MESSAGE AND ANTI-MESSAGE (GENOMIC) RNA FROM A DEFECTIVE VESICULAR OMATITIS VIRUS PARTICLE. (Eng.) Lazzarini, R. A. atl. Inst. Neurological Diseases and Stroke, thesda, Md. 20014); Weber, G. H.; Johnson, L. D.; amminger, G. M. *J. Mol. Biol.* 97(3):289-307; 75.

nember of a new class of defective vesicular omatitis virus particles, DI_{011}, which contains ssenger RNA and genomic RNA covalently linked, s characterized. Annealing and electron micro- opic analyses indicated that the complementary quences of this duplex were covalently linked a hairpin structure. Approximately half of the quences found in this RNA were normal genomic quences found in the RNA of the infectious virus. e other half, the complement of the former, were ssage sequences that were not found in the infec- ous virus. Within the particle, the RNA existed a single-stranded ribonucleoprotein complex, 35 μm in length. Upon deproteinization the RNA llapsed into a self-complementary double stranded plex, 0.33 μm in length. The possible relevance covalently linked message and genomic sequences the mechanism of vesicular stomatitis virus plication is discussed.

55 ALTERATIONS OF ENZYMES ASSOCIATED WITH PLASMA MEMBRANES AND CELLULAR ORGANELLES RING INFECTION OF CV-1 CELLS WITH YABA TUMOR POX- RUS. (Eng.) Milo, G. E., Jr., (Coll. Vet. Med., io State Univ., Columbus); Yohn, D. S. *Cancer Res.* (1):199-206; 1975.

enotypic changes in enzymes associated with the asma membrane of Yaba tumor poxvirus-infected cells volved in the formation of microaggregates were alyzed. Infected and uninfected Ceropithecus mon- y kidney cell (CV-1) cultures which were treated or t treated with hormones were subjected to fractiona- on on 8% acrylamide gel. Various enzymes were as- yed on 8% gel, and enzyme activity was quantitated spectrophotometry. Cytoplasmic membrane underwent lyacrylamide gel electrophoresis. Cell cultures re infected at a multiplicity of 1 or 10 focus- rming units/cell in medium containing 0.1 mM cal- um, and hormones solubilized in ethanol were added the medium (1 μg/ml). Magnesium chloride and man- nese chloride were dissolved in the overlay media 1 mM and added to media deficient in the Mn^{2+} and $^{2+}$. Foci formation was dependent on cell passage vel, incubation temperature and calcium concentra- on in the medium. Resistance of cells beyond pas- ge 35 was reversed by maintaining calcium at 0.1 mM by the addition of cortisone acetate, hydrocorti- ne or estradiol-17β (each 1 μg/ml). Foci formation resistant cells made susceptible was almost 50% hibited by methyltestosterone (1 μg/ml), and com- ete inhibition occurred with 1 μg/ml with proges- terone, 1 μg/ml aldosterone, 1 μg/ml dexamethasone and estrone (0.01, 0.1 and 1 μg/ml). Examination of changes in enzyme activities of membrane-associated enzymes and protein patterns in infected susceptible and resistant cells made susceptible with calcium showed that membrane protein composition changed during foci formation. In infected resistant cells made susceptible, alkaline phosphatase activity was virtually undetectable. Rearrangement and/or formation of additional membrane-associated isoenzymes was also demonstrated in infected cultures. Resistance to foci formation occurred during passages 45-50 and was reversed by the addition of hormones. It is suggested that this enhancement by hormones may be associated with alterations in cell membranes.

3256 PURIFICATION OF SV-40 MESSENGER RNA BY HYBRIDIZATION TO SV-40 DNA COVALENTLY BOUND TO SEPHAROSE. (Eng.) Gilboa, E. (Weizmann Inst. Science, Rehovot, Israel); Prives, C. L.; Aviv, H. *Biochemistry* 14(19):4215-4220; 1975.

The purification and properties of Simian virus 40 (SV40) DNA covalently bound to Sepharose and its use in the purification of SV40-specific (mRNA) are reported. SV40 DNA sheared form was coupled in a stable covalent bond to cyanogen bromide-activated Sepharose. The DNA-Sepharose was then hybridized to RNA complementary to SV40 DNA and to RNA from SV40-infected BS-C-1 cells. In other experiments, the hybridization procedures were carried out using SV40 DNA immobilized on nitrocellulose filters. The virus-specific RNA selected in the hybridization experiments was separated by polyacrylamide gel electrophoresis, and mRNA preparations were translated using cell-free extracts from wheat germ. Under the conditions used, at least 80% of the SV40 DNA was bound to Sepharose. The $t_{1/2}$ of the hybridization of SV40 complementary RNA to SV40 DNA-Sepharose was one hour, the rate being sufficiently rapid to purify SV40 sequences from solutions containing as little as 0.05-0.1 μg/ml. Nonspecific hybridization of RNA was in the range of 0.1-0.2% of the total input RNA. The DNA-Sepharose was fairly stable and could be reused several times to purify RNA. Although the virus-specific RNA obtained using SV40 DNA immobilized on nitrocellulose filters comprised the same percent of input RNA as was observed using SV40 DNA-Sepharose, a greater loss of virus-specific RNA was observed with the former. The virus-specific RNA when added to the cell-free extracts from wheat germ directed the synthesis of the major viral structural protein vp-1. Thus, the hybridization of RNA to DNA immobilized on a solid matrix proceeds with sufficient rapidity to be useful both for analytical studies of RNA and for the preparation of biologically active mRNA.

3257 ISOLATION AND PARTIAL CHARACTERIZATION OF SINGLE-STRANDED ADENOVIRAL DNA PRODUCED DURING SYNTHESIS OF ADENOVIRUS TYPE 2 DNA. (Eng.) Lavelle, G. (Oak Ridge Natl. Lab., Oak Ridge, Tenn. 37830); Patch, C.; Khoury, G.; Rose, J. *J. Virol.* 16(4):775-782; 1975.

3258 IMMUNE FLUORESCENT STUDY OF THE MIGRATION OF ADENOVIRUS 5 IN HeLa CELL CYTOPLASM DURING THE PHASE OF PENETRATION. (Fre.) Lyon, M. (Equipe de Recherche n° 124 du CNRS, Unité de Virologie, INSERM, 1, place Pr Joseph-Renaut, 69008 Lyon, France); Chardonnet, Y. *C. R. Acad. Sci.* [*D*] *(Paris)* 280(16):1919-1922; 1975.

3259 STUDIES ON SIMIAN VIRUSES AS POSSIBLE CONTAMINANTS OF INACTIVATED VIRUS VACCINES. I. DIRECT AND SEROLOGIC DETECTION OF SIMIAN ADENOVIRUS SV_{20}. (Ger.) von Mettenheim, A. E. (Paul-Ehrlich-Institut, D-6 Frankfurt a.M., Paul-Ehrlich-Str. 42-44, West Germany). *Zentralbl. Bakteriol.* [*Orig. A*] 232(2-3):131-140; 1975.

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3262 C TYPE MURINE LEUKAEMIA VIRUS PARTICLES IN TETRAPARENTAL AKR ↔ CBA CHIMAERAS. (Eng.) Wills, E. J. (Clinical Res. Centre, Watford Road, Harrow HA1 3UJ, Middlesex, England); Tuffrey, M.; Barnes, R. D. *Clin. Exp. Immunol.* 20(3):563-569; 1975.

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3266 INABILITY OF HUMAN 'K' CELLS TO TRANSFOR WITH EPSTEIN-BARR-VIRUS (EBV) [abstract] (Eng.) Peter, H. H. (Div. Clin. Immunol. Hematol MHH, Hannover, West Germany); Diehl, V.; Knoop, F Kalden, J. R. *Fed. Proc.* 34(3):987; 1975.

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3281 INDUCTION OF CUTANEOUS OR SUBCUTANEOUS FIBROBLASTIC TUMORS OF THE OCHOTON AFGHAN (*OCHOTONA RUFESCENS RUFESCENS*) BY INOCULATION OF BOVINE PAPILLOMA VIRUS. (Fre.) Puget, A. (Laboratoire de Pharmacologie et de Toxicologie Fondamentales du CNRS, 205, route de Narbonne, 31078 Toulouse, France); Favre, M.; Orth, G. *C. R. Acad. Sci. [D] (Paris)* 280(24):2813-2816, 1975.

3282 BINDING OF POLYOMA DNA TO EMPTY POLYOMA CAPSIDS [abstract]. (Eng.) Aposhian, H. V. (Univ. Maryland Sch. Med., Baltimore); Kelly, T. J., Jr.; Thayer, R. E. *Fed. Proc.* 34(3):527; 1975.

3283 TRANSPLANTABLE HAMSTER TUMORS INDUCED WITH THE BK VIRUS. (Eng.) Nase, L. M. (Dept. Clinical Microbiology, Univ. Of Kuopio, 70100 Kuopio 10, Finland); Mantyjarvi, R. A. *Acta Pathol. Microbiol. Scand.* [*B*] 83B(4):347-352; 1975.

3284 PHYSICAL MAP OF THE BK VIRUS GENOME. (Eng.) Howley, P. M. (Natl. Inst. Allergy and Infectious Diseases, Bethesda, Md. 20014); Khoury, G.; Byrne, J. C.; Takemoto, K. K.; Martin, M. A. *J. Virol.* 16(4):959-973; 1975.

3285 THE SPECIFIC IMMUNE-PRECIPITATION OF INTRACELLULAR PRECURSOR-LIKE POLYPEPTIDES OF RAUSCHER LEUKEMIA VIRUS [abstract]. (Eng.) Naso, R. B. (Univ. Texas Syst. Cancer Cent., M. D. Anderson Hosp. Tumor Inst., Houston); Arcement, L. J.; Arlinghaus, R. B. *Fed. Proc.* 34(3):527; 1975.

3286 ISOLATION AND CHARACTERIZATION OF VIRUSES FROM NATURAL OUTBREAKS OF RETICULOENDOTHELIOSIS IN TURKEYS. (Eng.) Sarma, P. S. (Natl. Cancer Inst., Bethesda, Md. 20014); Jain, D. K.; Mishra, N. K.; Vernon, M. L.; Paul, P. S.; Pomeroy, B. S. *J. Natl. Cancer Inst.* 54(6):1355-1359; 1975.

3287 COMPARATIVE ULTRASTRUCTURAL STUDY OF FOUR RETICULOENDOTHELIOSIS VIRUSES. (Eng.) Kang, C. Y. (Univ. of Texas Southwestern Medical Sch., Dallas, Tex. 75235); Wong, T. C.; Holmes, K. V. *J. Virol.* 16(4):1027-1038; 1975.

3288 DETECTION OF REVERSE TRANSCRIPTASE IN HUMAN BREAST TUMOURS WITH POLY(Cm)·OLIGO(dG). (Eng.) Gerard, G. F. (St. Louis Univ. Sch. Medicine, St. Louis, Mo. 63110); Loewenstein, P. M.; Green, M.; Rottman, F. *Nature* 256(5513):140-143; 1975.

3289 CELL SURFACE CHANGES ACCOMPANYING VIRAL TRANSFORMATION: *N*-ACETYLNEURAMINIC ACID ECTOTRANSFERASE SYSTEM ACTIVITY. (Eng.) Spataro, A. C. (Univ. Rochester Sch. Medicine and Dentistry, Rochester, N. Y. 14642); Morgan, H. R.; Bosmann, H. B. *Proc. Soc. Exp. Biol. Med.* 149(2):486-490; 1975.

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3291 HIGH AFFINITY BINDING OF SIMIAN VIRUS 40 T ANTIGEN TO SV40 DNA [abstract]. (Eng.) Spillman, T. (Univ. Illinois, Urbana); Spomer, B.; Hager, L. *Fed. Proc.* 34(3):527; 1975.

3292 POSSIBLE NUCLEASE ACTIVITY OF THE T-ANTIGEN OF VIRUS SV-40. (Eng.) Shliankevich, M. A. (Inst. Experimental Clinical Oncology, Acad. Medical Sciences U.S.S.R., Moscow, U.S.S.R.);

Pirtskhalaishvili, D. S.; Prigozhina, T. B.; Drize, O. B.; Shapot, V. S. *Bull. Exp. Biol. Med.* 79(1): 46-49; 1975.

3293 DETECTION OF ENDONUCLEASE ACTIVITY IN SV-40 VIRUS T-ANTIGEN PREPARATIONS. (Rus.) Shliankevich, M. A. (Inst. Exper. Clin. Oncol., Acad. Med. Sci., Moscow, U.S.S.R.); Drize, O. B.; Shapot, V. S. *Dokl. Akad. Nauk S.S.S.R.* 221(4): 987-989; 1975.

3294 METHYLATED SV40 mRNAs. (Eng.) Aloni, Y. (Dept. Genetics, The Weizmann Inst. Science, Rehovot, Israel). *FEBS Lett.* 54(3):363-367; 1975.

3295 RELEASE OF A GROWTH FACTOR FOR SV40 VIRUS-TRANSFORMED CELLS BY RAT LIVER AND HEMI-CORPUS PERFUSIONS. (Eng.) Lipton, A. (Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, Pa. 17033); Roehm, C. J.; Robertson, J. W.; Dietz, J. M.; Jefferson, L. S. *Exp. Cell Res.* 93(1):230-234; 1975.

3296 AMINO ACID TRANSPORT SYSTEMS IN 3T3 AND SV3T3 MOUSE CELLS [abstract]. (Eng.) Cecchini, G. (Dep. Biol. Chem., Univ. Michigan, Ann Arbor); Lee, M.; Oxender, D. L. *Fed. Proc.* 34(3):556; 1975.

3297 INDEPENDENT REGULATION OF CELLULAR PRO-PERTIES IN THERMOSENSITIVE TRANSFORMATION MUTANTS OF MOUSE FIBROBLASTS. (Eng.) Rudland, P. S. (Imperial Cancer Res. Fund, PO Box 123, Lincoln Inn Fields, London WC2A 3PX, UK); Pearlstein, E.; Kamely, D.; Nutt, M.; Eckhart, W. *Nature* 256(5512) 43-46; 1975.

See also:

* (Rev): 3010, 3011, 3012, 3013, 3014, 3015, 3016, 3017, 3018, 3052, 3053, 3054, 3069
* (Chem): 3123, 3155, 3166
* (Immun): 3310, 3312, 3326, 3328, 3345, 334, 3352, 3354, 3355, 3356, 3358, 336, 3367, 3369, 3371, 3381, 3390, 339
* (Path): 3419, 3435, 3464, 3488

3298 IMMUNOLOGICAL STUDIES OF WOMEN WITH PRIMARY BREAST CARCINOMA. (Eng.) Jeejeebhoy, H. F. (Fox Chase Cancer Center, Philadelphia, Pa. 19111). *Int. J. Cancer* 15(6):867-878; 1975.

The ability of lymphocytes to inactivate breast tumor cells *in vitro* was tested as a criterion for distinguishing women who had residual disease after apparently complete surgical excision of breast carcinoma and its lymph node extensions (if any) from disease-free women. Thirteen women with breast lumps caused by fibrocystic disease and 16 individuals with breast carcinoma were studied. Controls consisted of 11 disease-free women. Sera and peripheral lymphocytes were obtained from the subjects for use in tests involving two target cell lines, which were derived from pleural effusions of women with metastatic breast cancer. Cells from cultures of seven primary tumors were also used as target cells. The lymphocyte preparations were tested for cytotoxicity against target cells in microcytotoxicity tests, and the preparations of sera were tested for ability to block, potentiate or leave unaffected the anti-tumor-cell activity of the lymphocyte preparations. Lymphoid cells from the test and control groups were comparable in their capacity to inactivate breast tumor cells *in vitro*. The anti-tumor effects of lymphocytes against autochthonous tumor cells were similar to those against cells of the established target cell lines. The lymphocytotoxic effects against breast tumor cells were not reflected against melanoma cells or normal fibroblasts. Sera from comparable numbers of women in each of the groups either blocked, potentiated or left unaffected the anti-tumor-cell cytotoxicity of their lymphocytes. Thus, doubt is cast on the validity of the hypothesis that a positive correlation exists between the presence of humoral blocking factors and *in vivo* tumor progression. The results are consistent, however, with the hypothesis that an inhibitory immune response to tumor-specific antigens could constitute a major defense mechanism against metastatic spread, despite its seeming ineffectiveness with respect to the primary tumor.

299 THE MECHANISM OF IMMUNORESISTANCE OF H(z1) MICE TO C57BL/6 TUMORS. (Eng.) Chauvenet, . H. (Duke Univ. Med. Cent., Durham, N.C.); Amos, . B. *Cell Immunol.* 17(2):477-486; 1975.

ellular immune responses of C57B1/6 mice and their ongenic mutant, H(z1), to native tumors were studied n order to help explain reciprocal skin graft rejection in the face of apparent serological identity. umors used were an ascites leukemia EL4 of C57B1 rigin, a melanoma B16 of C57B1/6J origin, and three ethylcholanthrene-induced fibrosarcomas of H(z1) rigin. One test for cellular immune response was ased on ^{51}Cr release from labeled tumor target ells, resulting from the lytic action of immune eritoneal exudate cells (IPEC). IPEC tp EL4 were repared in H(z1) or Balb/c mice. Cellular immune esponses were also determined by tests for susceptibility of strains of mice to the different tumors nd for ability of IPEC to inhibit tumor growth n *vivo*. H(z1) mice showed resistance to EL4, and B16 was a weaker immunogen than EL4 in H(z1) mice; B1/6J mice had no detectable resistance to any of the three methylcholanthrene-induced fibrosarcomas. These results indicate less stringent requirements for host-tumor susceptibility than for skin graft compatibility between H(z1) mice and C57B1/6J mice. The *in vitro* secondary cell-mediated cytolytic response of H(z1) mice to EL4 was specific and was of similar magnitude to the Balb/c secondary *in vitro* cytolytic response to the same tumor. Thus, cellular immunity, as assayed *in vitro*, need not correlate with humoral antibody production. H(z1) IPEC against EL4 tumor were capable of inhibiting EL4 growth *in vivo* in F_1(H(z1) x C57B1) mice, which normally have no resistance to EL4. Further, IPEC against EL4 were capable of *in vitro* cytolysis of normal B1/6J cells, indicating the presence of common antigens on B1/6J and EL4 to which H(z1) responds. B1/6J lymph node cells, but not H(z1) cells, were able to competitively inhibit EL4 lysis in the *in vitro* cytolysis of EL4 by Balb/c IPEC against EL4. This provides an additional means of distinction between H(z1) and C57B1/6J normal cells.

3300 SOME IMMUNOLOGIC CHARACTERISTICS OF CARCINOMA OF THE COLON AND RECTUM. (Eng.) Elias, E. G. (Dept. General Surgery, Roswell Park Memorial Inst., Buffalo, N.Y.); Elias, L. L. *Surg. Gynecol. Obstet.* 141(5):715-718; 1975.

The WBC migration-inhibition assay was used to assess *in vitro* cell mediated immunity in patients with surgically staged carcinoma of the colon and rectum. Tumor cells and extracts were used in both the autologous and the homologous systems. The study was doubly controlled by the use of WBC from normal healthy volunteers and by autologous intestinal mucosa cells and extracts. The WBC of patients were significantly sensitized to autologous tumor cells but not to homologous tumor cells or extracts when compared with the WBC of normal healthy volunteers. Leukocytes of patients tested with autologous tumors or mucosa showed that only those of patients with Dukes C classification were significantly sensitized to their tumors. These results suggest that carcinomas of the colon and rectum are heterogenous tumors.

3301 A LONG-TERM ^{51}CHROMIUM ASSAY FOR *IN VITRO* CELL-MEDIATED TUMOR IMMUNITY. CORRELATION WITH SIMULTANEOUSLY PERFORMED MICROPLATE ASSAYS. (Eng.) Steele, G., Jr. (Wallenberg Lab., Univ. Lund, Lund, Sweden); Sjogren, H. O.; Lannerstad, O.; Stadenberg, I. *Int. J. Cancer* 16(4):682-693; 1975.

In vitro assays of cell-mediated tumor immunity utilizing ^{51}Chromium (^{51}Cr) labeling of cultured adherent solid tumor cells were designed which allowed an effector cell/target cell incubation time of 48 hr without overriding spontaneous ^{51}Cr release. In a series of 16 consecutive experiments, blood lymphocytes from healthy human donors, from patients with tumors unrelated to the cultured tumor target cells, and from colon carcinoma and melanoma patients

were tested for their cytotoxic effects on various target cell pairs, human colon carcinoma, melanoma, or skin fibroblasts. The same reagents were used in simultaneously performed microplate and ^{51}Cr assays. Results obtained by visual counting of microplate tests and by 24 hr assays of ^{51}Cr release or ^{51}Cr retention correlated in 20/25 effector-cell/target-cell combinations. In a series of six consecutive experiments, lymph-node cells from untreated Wistar/Furth rats, and rats bearing either chemically-induced colon carcinoma NG-W1 or polyoma virus-induced sarcoma P-W13 were tested for cytotoxicity on syngeneic rat colon carcinoma and sarcoma target cells. Criss-cross type experiments were performed by microplate and ^{51}Cr techniques done in parallel. Results obtained by visual counting of microplate tests and by 48 hr assays of ^{51}Cr release or ^{51}Cr retention correlated in 15/18 effector-cell/target-cell combinations. The ^{51}Cr assay is less tedious than microplate tests with visual counting and, at least with human effector cells on human target cells, requires a shorter incubation period to obtain similar cytotoxic effects.

3302 SYNERGY BETWEEN SUBPOPULATIONS OF NORMAL MOUSE SPLEEN CELLS IN THE *IN VITRO* GENERATION OF CELL-MEDIATED CYTOTOXICITY SPECIFIC FOR "MODIFIED SELF" ANTIGENS. (Eng.) Hodes, R. J. (Immunology Branch, Natl. Cancer Inst., Bethesda, Md. 20014); Hathcock, K. S.; Shearer, G. M. *J. Immunol.* 115(4):1122-1125; 1975.

Responding lymphoid cells were cultured *in vitro* with irradiated trinotrophenyl (TNP)-modified syngeneic spleen cells. Direct cell-mediated cytotoxicity developed. This occurred specifically for target cells bearing both the TNP moiety and histocompatibility determinants of the modified sensitizing cell. Two subpopulations of normal mouse spleen cells were shown to synergize in the *in vitro* generation of specific cell-mediated cytotoxicity to these "modified self" antigens. The synergizing populations were nylon wool column-adherent and column-nonadherent fractions of normal mouse spleen. When mixtures of these two cell populations were cultured *in vitro* with irradiated TNP-modified syngeneic spleen cells, greater cytotoxicity was generated than would be expected from the sum of cytotoxic activities generated in the two populations sensitized separately. The synergizing cell in the column-adherent population was resistant to lysis by rabbit anti-mouse brain serum, was distinct from the cytotoxic effector T lymphocyte, and was unresponsive to phytohemagglutinin; its synergizing function could not be replaced by peritoneal cells. The results suggest that it is a non-T cell which may be distinct from the macrophage.

3303 CELL-MEDIATED CYTOTOXICITY TO CHEMICALLY-INDUCED RAT TUMORS. (Eng.) Zoller, M. (Deutsches Krebsforschungzentrum Heidelberg, Institut fur Nuklearmedizin, 69 Heidelberg, West Germany); Price, M. R.; Baldwin, R. W. *Int. J. Cancer* 16(4): 593-606; 1975.

Cell-mediated immune reactions against carcinogen-induced Wistar rat tumors were demonstrated by the *in vivo* microcytotoxity test. Lymph-node cells from syngeneic rats immunized against 4-dimethyl-aminoazobenzene-induced (po) hepatomas or 3-methyl cholanthrene-induced sarcomas were cytotoxic for cells of the immunizing tumor compared with the effects of normal lymph-node cells. Only a low level of cross-reactivity was detectable against target cells derived from other tumors. Conversely, lymph node cells from tumor-bearer rats were cross-reactive against a range of tumor cells, suggesting that the tumor-bearer was sensitized against a common antigen(s) as well as the individually specific antigen associated with these tumors. Lymph-node cells were reactive at an early time (from day 2) after tumor implantation and their cytotoxic potential persisted until terminal stages of tumor growth. Spleen cells from tumor-bearer and tumor-immune donors also exhibited comparable cytotoxic reactivities of the same specificity as that shown by lymph node cell preparations. These findings are discussed in relation to the development of cell-mediated immune responses in the tumor-bearing rat and in immunized rats which are capable of rejecting transplanted tumor cells.

3304 CHARACTERISTICS OF THE EFFECTOR CELLS MEDIATING CYTOTOXICITY AGAINST ANTIBODY-COATED TARGET CELLS. II. THE MOUSE NONADHERENT K CELL. (Eng.) Greenberg, A. H. (Middlesex Hosp., London, England); Shen, L.; Walker, L.; Arnaiz-Villena, A.; Roitt, I. M. *Eur. J. Immunol.* 5(7):474-480; 1975.

An attempt was made to clarify apparent species differences in nonphagocytic effector cells of mice and humans in that such cells in mice are found in an inherent population of cells while such cells in humans are found in nonadherent populations as well. The particular effector cells were detected by their cytotoxicity for antibody-coated chicken red blood cells (CRBC). Spleen cell preparations from nonimmune BALB/c or (BALB/c x C57BL/6)F_1 mice were treated with a combination of carbonyl iron and passage through glass beads to yield a fraction which contained less than 1% of monocytes and polymorphonuclear leukocytes, was incapable of phagocytosing SRBC-antibody-complement complexes, and contained reduced proportions of immunoglobulin-bearing cells. Cytotoxicity assays were carried out with rabbit antibody-coated CRBC as the target cells, where the antibody used was prepared against CRBC or consisted of Fab of rabbit anti-CRBC antibody coupled with dinitrobenzene sulfonic acid. The results showed that cells present in the nonadherent spleen cell preparation were capable of killing antibody-coated CRBC. This nonphagocytic effector cell, referred to as the nonadherent K (killer) cell, is distinguished from the previously described nonphagocytic myeloid K cell by its relatively weak surface adherence properties and low concentration within the mouse spleen. The ability of the nonadherent K cells to kill CRBC in the presence of rabbit antiserum differed from that of whole spleen cell preparations in that over 15 times higher concentrations of antiserum were required before optimal killing was reached, and sig

ficant cytotoxicity could be demonstrated with whole spleen cells at low antiserum concentrations where lymphoid preparations were virtually inactive. The nonadherent K cell was further characterized by its relatively large size, lack of theta or immunoglobulin determinants, the presence of Mg^{++}-independent complement receptors, affinity for aggregated IgG_2 myeloma proteins, inhibition by cytochalasin B and good survival in cell culture. The results indicate that the species differences are quantitative rather than qualitative, since it could be demonstrated that nonadherent lymphoid effector cells exist in mice as well as in humans.

3305 SPECIFIC ANTI-TUMOR RESPONSES BY CULTURED IMMUNE SPLEEN CELLS. I. *IN VITRO* CULTURE METHOD AND INITIAL CHARACTERIZATION OF FACTORS WHICH BLOCK IMMUNE CELL-MEDIATED CYTOTOXICITY *IN VITRO*. (Eng.) Nelson, K. (Univ. Washington Sch. Med., Seattle); Pollack, S. B.; Hellstrom, K. E. *Int. J. Cancer* 15(5):806-814; 1975.

Culture supernatants of spleen cells from normal BALB/c mice or mice bearing transplanted, syngeneic sarcomas were assayed for their ability to inhibit (block) the antitumor cytotoxicity of immune lymphoid cells or to mediate antiserum-dependent cellular cytotoxicity (ADC) by control lymphoid cells. Spleen cell culture supernatants from mice bearing a 3-methylcholanthrene-induced tumor blocked the cytotoxicity of lymphoid cells immunized to that tumor; cell-mediated cytotoxicity to a non-cross-reacting tumor was not inhibited. In ten similar experiments with several different tumors, culture supernatants from tumor-bearing mice exhibited a mean blocking activity of 82% with the blocking specific for the tumor borne by the spleen donor. Ten of 13 supernatants from tumor-bearing mice also mediated ADC when assayed at dilutions of 10^{-2} and higher. Neither blocking activity nor ADC activity required the addition of endogenous antigen. Blocking activity was not detected in culture supernatants after lysis of Θ-positive cells with antiserum and complement. The activity was removed by passing the culture supernatants through an antimouse immunoglobulin affinity column and could be recovered in a 3 M NaSCN eluate of the column. It was not established whether there is an active synthesis or a passive release *in vitro* of the factors mediating the blocking and ADC activities. However, the evidence suggests synthesis.

3306 SPECIFIC ANTI-TUMOR RESPONSES OF CULTURED IMMUNE SPLEEN CELLS: III. FURTHER CHARACTERIZATION OF CELLS WHICH SYNTHESIZE FACTORS WITH BLOCKING AND ANTISERUM-DEPENDENT CELLULAR CYTOTOXIC (ADC) ACTIVITIES. (Eng.) Nelson, K. (Wallenberg Lab., Univ. Lund, Fack, 5-22007 Lund, Sweden); Pollack, S. B.; Hellstrom, K. E. *Int. J. Cancer* 16(4): 539-549; 1975.

The effects of different cell-types on the tumor-specific activities of supernatants from spleen cells were studied. Spleen cells from BALB/c mice bearing syngeneic, methylcholanthrene-induced (sc) sarcomas were cultured *in vitro*. In agreement with previous observations, the supernatants suppressed specific lymph-node cell-mediated cytotoxicity directed against the respective neoplasm (blocking factors) and they induced specific antibody-dependent cellular cytotoxicity (ADC) mediated by lymph-node cells from non-immune mice. Spleen cells passed through columns of Sephadex G-10, which removed plasma cells and macrophages, no longer synthesized factors with ADC activity though synthesis of blocking factors continued. However, lysis of Thy-1-positive cells with antiserum and complement did abolish the synthesis of blocking factors. Spleen cells from tumor-bearing mice were then enriched for Thy-1-positive cells by selective removal of macrophages and plasma cells on G-10 columns and of immunoglobulin (Ig)-bearing cells on anti-mouse Ig affinity columns. This T-cell-enriched population synthesized blocking factors and restored blocking factors synthesis in cultures depleted of Thy-1-positive cells. Similarly enriched spleen cells from normal control mice did not synthesize tumor-specific blocking factors but partially restored synthesis of blocking factor in tumor-bearer spleen cultures depleted of Thy-1-positive cells. The findings suggest that thymectomy might depress the formation of blocking factors. Cells retained by G-10 columns are involved in *in vitro* production of ADC. Lymphocytes carrying the Thy-1 marker are implicated in the synthesis of blocking factors.

3307 SPONTANEOUS AND INDUCED TUMOR INCIDENCE IN GERMFREE "NUDE" MICE. (Eng.) Outzen, H. C. (Fox Chase Cent. Cancer Med. Sci., Philadelphia, Pa.); Custer, R. P.; Eaton, G. J.; Prehn, R. T. *J. Reticuloendothel. Soc.* 17(1):1-9; 1975.

A colony of conventional and germfree "nude" (nu/nu) mice and their heterozygous (nu/+) littermates were investigated with respect to spontaneous and 3-methylcholanthrene (MCA)-induced tumor incidence. A total of 308 male and female nu/+ and 261 male and female "nude" mice were maintained germfree for over 20 mo with routine sterility monitoring and observation. Many of the "nude" colony received mouse skin allografts to demonstrate their general T-cell incompetence. The grafts themselves did not affect tumor incidence or latency. MCA was implanted (5% pellets) in six "nude" and six nu/+ mice, which were then observed for six months. The germfree "nude" mouse colony developed 22 "spontaneous" lymphoreticular tumors with a mean latency $\pm$ standard deviation of 57 wk $\pm$ 1.56 wk. Three mammary tumors were also observed despite the absence of the murine mammary tumor virus. The spontaneous tumors were not sex-related. The germfree nu/+ females showed no tumors at all by the cut-off date. The comparatively short-lived conventional "nude" colony showed only two lymphoreticular tumors, which was attributed to the long latency of spontaneous tumor incidence. The conventionally maintained nu/+ colony developed several spontaneous neoplasms, the most prominent of which were 12 mammary tumors, with a latency $\pm$ SD of 60 wk $\pm$ 1.26 wk. The absence of these tumors in the germfree nu/+ females was thought to be due to the elimination of the mammary

tumor virus. Four of the six mice in both the "nude" and nu/+ germfree MCA-treated groups developed fibrosarcomas with no significant difference in the latency periods. The authors suggest that the germfree "nude" mouse, deficient in all thymus-derived, cell-mediated (T cell) immunologic responses, is a good model for testing immunosurveillance and/or immunostimulation as active modulators of tumor regression of development. The large number of spontaneous neoplasms in the germfree "nudes" was not felt to be necessarily related to, or to preclude, either the immunosurveillance or immunostimulation hypotheses. Although the results of the MCA-induction experiment implied that immunosurveillance was not effective, the authors warn that the dosage of MCA was greater than the threshold dose, and that further investigation is needed to clarify the matter.

3308 INCREASED INCIDENCE OF MALIGNANCY DURING CHRONIC RENAL FAILURE. (Eng.) Matas, A. J. (Dept. Surg., Univ. Minnesota, Minneapolis); Simmons, R. L.; Kjellstrand, C. M.; Buselmeier, T. J.; Najarian, J. S. *Lancet* 1(7912):883-885; 1975.

The incidence of cancer in 646 dialysis/transplant patients before uremia developed, during the period of progressive uremia, and post-transplantation was compared. Ten tumors (three breast, two kidney, one leukemia, one lung, one insulinoma, one thyroid, one cervix *in situ*) developed in nine patients during the period of progressive uremia, a significant increase over the expected number in the age-matched general population (148/100,000/yr). Six of these patients have received transplants and have no evidence of recurrent disease six months to four years post-transplantation. Eleven *de-novo* tumors have developed in 530 transplant recipients (four cervix *in situ*, two skin, two reticulum-cell sarcomas, one lip, one dysgerminoma, one colon)--a significant increase over the age-matched general population (102/100,000/yr). The cancers in the uremic patients are relatively common types of mesenchymal tumors while the cancers in the transplant recipients are epithelial and lymphoproliferative. This difference may reflect the presence of the graft in the transplant patient or may be due to different patterns of immunosuppression in these two populations.

3309 LOSS OF MARROW ALLOGRAFT RESISTANCE IN MICE WITH TRANSPLANTED METHYLCHOLANTHRENE-INDUCED SARCOMAS. (Eng.) Kumar, V. (Boston Univ. Sch. Medicine, Boston, Mass. 02118); Bennett, M. *J. Natl. Cancer Inst.* 55(2):489-492; 1975.

To determine if the effector cells responsible for rejection of marrow stem cell allografts are suppressed in mice bearing tumors, C57BL/6 (B6) mice were subjected to s.c. transplants of 10^5 syngeneic 3-methylcholanthrene (MCA)-induced sarcoma cells; and when the resulting tumors reached 2.0-2.5 cm in diameter, these mice and control B6 and (BALB/c x A)F_1 (CAF_1) uninoculated animals were irradiated and infused i.v. with 2.5 x 10^6 BALB/c marrow cells. Four days later, the spleen cells were harvested from the primary recipients and assayed for content of donor marrow-derived stem cells. The assay was carried out by retransplanting by i.v. infusion one-third equivalent of the primary recipient spleen into irradiated CAF_1 secondary hosts which had been immunized 7 days previously by i.v. injection of 10^6 B6 spleen cells to prevent growth of any surviving B6 stem cells transferred from the irradiated primary recipient. Proliferation of progeny of implanted cells in secondary recipient spleens was determined by measuring the incorporation of ^{125}I-iodo-2'-deoxyuridine (IUDR) five days after spleen cell regrafting. Under these conditions the IUDR labels primarily erythropoietic cells. The uptake values thus represented the production of new erythropoietic progenitor cells in the spleens of the primary hosts. It was found that the BALB/c marrow stem cells grew as well in allogeneic B6 mice bearing tumors as in histocompatible CAF_1 primary hosts, but were rejected by non-tumor-bearing B6 controls. The results of further tests indicated the absence of "suppressor cells" in spleens in tumor-bearing mice, which could have inhibited the rejection of the allogeneic bone marrow cells. It was concluded that transplanted syngeneic MCA-induced sarcomas abrogated the ability of mice to reject allogeneic marrow stem cells.

3310 LYMPHOCYTE SURFACE RECEPTORS AND LEUKEMIA VIRUS-INDUCED IMMUNOSUPPRESSION. (Eng.) Friedman, H. (Albert Einstein Med. Cent., Philadelphia, Pa.); Kateley, J. R. *J. Clin. Pathol.* 63(5): 735-747; 1975.

The effects of Friend leukemia virus (FLV) on the number and distribution of lymphocytes bearing immun globulin surface receptors was studied in spleens an lymph nodes of Balb/c mice in order to determine how FLV infection depresses the immune response of mice to SRBC and *Escherichia coli* lipopolysaccharide (LPS) antigens. Immunofluorescence techniques were used to measure surface immunoglobulin receptors in single-cell suspensions of spleen and lymph nodes from normal and FLV-infected animals. The response to both antigens was depressed in FLV-infected mice, and the major effect appeared to be impairment of B cell function early in the course of infection. Immunofluorescent analysis of spleen and lymph node cells from mice infected with FLV for a few days showed a marked decrease in the percentage of spleen cells with immunoglobulin receptors, and a marked decrease in splenocytes with theta antigen. The number of spleen cells was either unchanged or slightly increased. Within 2-2½ wk, all of the splenocytes were positive for FLV-associated antigens. In the lymph nodes, increases in the percentages of immunoglobulin positive- and theta-positive cells were see and the percentage of lymph node cells with FLV-antigens was lower and reached only 32% after 17 days. Immunoglobulin-polar capping responses of both splee and lymph node cells were impaired equally, and paralleled the development of immuno-suppression. The results indicate that FLV infection altered the response of immunocompetent cells to T-dependent and -independent antigens, and suppressed normal functional activity of the immune system.

3311 GYNECOLOGIC MALIGNANCIES IN IMMUNOSUPPRESSED ORGAN HOMOGRAFT RECIPIENTS.
(Eng.) Porreco, R. (Univ. Colorado Sch. Med., Denver); Penn, I.; Droegemueller, W.; Greer, B.; Makowski, E. *Obstet. Gynecol.* 45(4):359-364; 1975.

Data collected by the Denver Transplant Tumor Registry show that immunosuppressed organ homograft recipients have a 5 to 6% incidence of *de novo* malignancies at some time after transplantation. Gynecologic cancers were encountered in 21 of 224 patients (9%) with these tumors. The predominant lesion was carcinoma of the cervix (18 cases), of which 16 were intraepithelial and two were invasive. All 18 patients had been recipients of kidney homografts; the mean time interval from renal transplantation to diagnosis of carcinoma was 38 mo (range, 6-97 mo). Of the major immunosuppressive agents, azathioprine and prednisone had been administered to all patients. The lesions were treated by hysterectomy in 12 instances, side conization in six, and cryosurgery in one, with one patient having wide conization followed later by hysterectomy for recurrence of the lesion. Four patients died, two from homograft rejection, one from metastases, and one from an unrelated infection. Gynecologic malignancies have also been encountered in nontransplant patients who were treated with immunosuppressive agents or cancer chemotherapy. All such individuals require gynecologic examination before commencement of treatment and at regular intervals thereafter so that malignancies may be diagnosed at an early stage and treated effectively. Most neoplasms respond well to conventional cancer therapy, but high-grade malignancies may necessitate reduction or cessation of immunosuppressive therapy as well.

3312 SPECIFIC SUSCEPTIBILITY OF SENSITIZED (MEMORY) B CELLS TO SUPPRESSION AND ANTIGENIC ALTERATION BY MURINE LEUKEMIA VIRUS. (Eng.) Cerny, J. (Harvard Sch. Public Health, Boston, Mass); Vaner, E. B. *J. Immunol.* 114(2):571-580; 1975.

To obtain evidence for the hypothesis that Friend virus (FV) infects and inhibits sensitized (memory) cells but not virgin immunocompetent cells, experiments were carried out involving BALB/c mice infected with different leukemia viruses and immunized with different antigens. The viruses used were Friend virus and Moloney leukemia virus (MuLV-M); the antigens were *Vibrio cholerae* vaccine and SRBC. Isologous antiserum against FV-induced cell membrane antigen (FVMA) was prepared by repeated immunization of BALB/c mice with virus vaccine and with isologous FV-infected spleen cells. The kinetics and magnitude of the specific vibriolytic plaque-forming cells (PFC) response in the spleen following a single primary immunization with the cholera vaccine showed no difference in the normal and FV-infected leukemic mice. However, the secondary response of sensitized FV-infected mice was greatly inhibited as compared to that of primed mice that were not infected. As with FV infection, MuLV-M infection selectively inhibited the secondary PFC response to cholera vaccine, although the primary response was also inhibited in the MuLV-M-infected mice. The degree of immunosuppression due to FV priming was comparable at various intervals, indicating that the immunologic memory to cholera antigen and the susceptibility of the memory to viral suppression is a long term phenomenon. Hemolytic PFC response to a single immunization with SRBC (an antigen to which laboratory mice have a natural immune background) was suppressed by infection with both viruses in a manner similar to the suppression of the secondary vibriolytic response. The suppressive effect of FV on the different immune responses was correlated with the appearance of FVMA on respective individual PFC from the spleen. The FVMA was detected by inhibition of PFC in the presence of specific anti-FVMA antiserum and complement. The findings thus indicated an absolute correlation between viral suppression of a given clone of immunocompetent cells and antigenic alteration of individual antibody-forming cells due to virus infection. Furthermore, the absence of both functional inhibition and virus-induced antigen in the primary immunocompetent cells and the presence of both of these virus-related functions in the memory cells strongly suggests that the latter are selectively susceptible to oncornavirus.

3313 ALTERATION OF IMMUNOGLOBULIN PHENOTYPE IN CELL CULTURE-ADAPTED LINES OF TWO MOUSE PLASMACYTOMAS. (Eng.) Hausman, S. J. (Gerontology Res. Center, Baltimore City Hospitals, Baltimore, Md. 21224); Bosma, M. J. *J. Exp. Med.* 142(4):998-1010; 1975.

Murine plasmacytomas were adapted to continuous *in vitro* culture by alternate passage between culture and animal. BALB/c mice congenic for different immunoglobulin (Ig) allotypes were used in these studies. For animal passage, each plasmacytoma was grown in congenic BALB/c mice having a different allotype from that of the tumor Ig. To facilitate the handling of tumor cells, plasmacytomas were injected ip into each new host mouse to induce ascites. Tumor cells were considered to be fully adapted to culture after five successive *in vitro* passages in spinner culture. $(NH_4)_2SO_4$ precipitation and DEAE-cellulose chromatography were used to obtain 7S Ig from pooled sera of the plasmacytoma-bearing mice. Salt precipitation and fractionation on Bio-Gel A-1.5m Agarose were used to obtain the IgM. Appropriate antisera were used to identify the Ig allotypes produced by the tumors before and after adaptation. Studies of the kinetics of adaptation revealed a selection for growth of variant plasmacytoma cells. For example, plasmacytoma MOPC 173, when placed in spinner culture for the third time, showed a decline in cell count from the level of 6.0×10^8 for the original seeding to less than 3×10^4 living cells after 17 days of culture. However, over the next 20 days, the number increased exponentially to greater than 10^7 cells, and extrapolation of the growth back to zero time indicated that less than 50 cells gave rise to the altered line. This meant that only about one in 10^7 cells of the starting population could grow in culture, and that such cells must have been variant cells. The inclusion of an altered Ig phenotype among such cells explained the variant Ig-producing cell lines that

were observed in 2 of 6 different Ig-producing plasmacytomas that were adapted to culture. The first variant, an IgM-producing cell line (104-76), was adapted from a transplanted line of MOPC 104C that had stopped producing IgM with binding specificity for α1-3 Dextran. Unlike MOPC 104E, the IgM of 104-76 contained κ- instead of λ-light chains and probably contained an altered or different μ-heavy chain. A second variant (352-57) was found in an IgG_{2b}-producing tumor (MOPC 352) which was induced in a BALB/c mouse strain (CB-6) that carried Ig genes of the C57BL/Ka allotype. This cell line apparently switched from producing IgG_2b molecules of the C57BL allotype (H^9) and of a known idiotype to IgG_1 molecules of the BALB/c allotype (F^{19}) without the idiotype marker. The propagation of a biclonal plasmacytoma from the time of original tumor induction is not thought to be a likely explanation for these results. Rather, it appears that plasmacytoma variants were being dealt with, or that secondary tumors of host origin were being induced.

3314 TUMOUR REJECTION PROPERTIES OF SOLUBILIZED TSTA FROM AN SV40-INDUCED NEOPLASM. (Eng.) Law, L. W. (Natl. Cancer Inst., Bethesda, Md. 20014) Henriksen, O.; Appella, E. *Nature* 257(5523):234-235; 1975.

Ten consecutive, solubilized antigen preparations of a simian virus 40 (SV40)-induced sarcoma (mKSA) were examined for their ability to immunize syngeneic BALB/c mice against this neoplasm. The ten preparations constituted crude membrane, crude soluble, or Sephadex G-150-chromatographed F-2 and F-3 fractions from membranes of either the ascitic form (ASC) of mKSA or a tissue culture subline (TC) with a reduced tumor-inducing capacity. BALB/c mice, 8-12 wk old, were given two sc injections of antigen at 2-wk intervals. All ten antigen preparations effectively protected the mice against challenge with mKSA cells. mKSA(TC) and mKSA(ASC) were equally effective, indicating that they share the same SV40-specific tumor reaction antigens in spite of long-continued passage *in vitro* and *in vivo*. Protection was afforded at cell-challenge concentrations well above the median effective tumor dose of 10^2 cells. The degree of protection was in the range of that provided by a single sc injection of 10^5 or 10^6 mKSA-TC cells. *In vitro* specific lymphocyte stimulation was observed with low concentrations of two ASC antigen preparations. In the Winn assay, sensitized spleen cells from mice immunized with crude soluble mKSA could neutralize mKSA tumor cells. Immunization did not protect BALB/c mice against the syngenic plasma cell tumor Adj-PC5 or against the chemical carcinogen-induced tumor Meth A.

3315 IgM-INDUCED TUMOR CELL CYTOTOXICITY MEDIATED BY NORMAL THYMOCYTES. (Eng.) Lamon, E. W. (Sch. Medicine, Univ. Alabama, Birmingham, Ala. 35294); Whitten, H. D.; Lidin, B.; Fudenberg, H. H. *J. Exp. Med.* 142(2):542-547; 1975.

Because immunoglobulin M (IgM) from sera of mice whose Moloney sarcoma virus (MSV)-induced tumors had regressed was previously found to induce cytotoxicity by nonimmune spleen cells, the present study was carried out in which a comparable effect was looked for using IgM from MSV regressor mice and normal thymocytes instead of spleen cells. The IgM was prepared by chromatographic fractionation of pooled sera from adult BALB/c regressor mice. Cytotoxicity assays were carried out using a cell line derived from an MSV-induced tumor of a CBA mouse as the source of target cells. After incubation of target cells first with serially diluted IgM, then with added macrophage-deficient splenocytes or thymocytes, the reduction in number of target cells was determined by counting or chromium-release procedures. It was found that while a 1:10 dilution of the IgM (related to unfractionated serum) caused a 34% reduction in target cell count when normal CBA spleen cells were used; a 1:320 dilution caused a similar reduction (45%) when normal CBA thymus cells were used. Further, the titer for the IgM at an endpoint of 16% reduction in target cells was 640 when CBA spleen cells were used, 1,280, when CBA thymus cells were used. The findings were confirmed by results of chromium-release assays. There was no lysis shown by either IgM or thymus cells alone. It appeared that the thymocyte-induced cytotoxicity brought about by IgM was more efficient than that induced by the same number of splenocytes. Since T cells, which by themselves were not cytotoxic, could be induced to be cytotoxic against target cells coated with IgM, it appeared conceivable that IgM with specificity for target cells may be involved in other situations of T-cell-dependent *in vitro* cytotoxicity.

3316 IMMUNE PRECIPITATION OF IMMUNOGLOBULIN PRODUCING POLYSOMES FROM MOUSE MYELOMA CELLS. (Eng.) Laskov, R. (Hebrew Univ. Hadassah Med. Sch., Jerusalem, Israel); Mitelman, S. *J. Immunol.* 114(2):566-570; 1975.

A technique of immune precipitation of polysomes, used for quantitating the percentage of MPC-11 myeloma cells synthesizing Ig, is reported. Two cloned cell lines of MPC-11 myeloma, a producer and a nonproducer of IgG, were maintained in tissue culture and also as solid tumors in BALB/c mice. MPC-11 IgG protein was purified from ascitic fluid of mice bearing the IgG-producing tumor by ammonium sulfate precipitation and DEAE-cellulose chromatography and was used for precipitation of rabbit anti-IgG antiserum. The relative rate of IgG synthesis in myeloma cells was determined by labeling the cells with ^{3}H-leucine, disrupting them with Nonidet P-40, removing the nuclei and ribosomes by centrifugation, precipitating the supernatant with rabbit anti-melanoma IgG serum, and measuring the radioactivity of the precipitated material. The anti-IgG precipitated about 20% of the total protein produced in the cells. Polysomes were prepared by labeling cells with ^{3}H-uridine, disrupting the cells with Nonidet P-40, removing the nuclei by centrifugation, and either using the supernatant (cytoplasmic extract) as the source of polysomes or purifying the polysomes by centrifuging them from the cytoplasmic extract. Anti-IgG serum precipitated 11.9% of the RNA of the

extract (about 14.6% of the RNA of the purified lysosomes). This suggested the presence of nonpolysomal RNA in the cytoplasmic extract. The results of immune precipitation indicated that IgG-producing polysomes of myeloma cells can be precipitated with a yield comparable to that expected from the synthesis rate of IgG. The specificity of the reaction was demonstrated in separate tests involving the use of antisera to egg albumin and of cells not producing IgG. The RNA in the immune precipitates was separated and was analyzed by acrylamide gel electrophoresis. The results showed that the anti-IgG immune precipitate contained, in addition to the main species of ribosomal RNA (28S and 18S), RNA with heterogenous size, which was probably messenger RNA. The absence of discrete RNA peaks in the nonspecific precipitate obtained with anti-egg albumin antiserum indicated that the polysomes were specifically precipitated by anti-IgG. It is suggested that amplified synthesis of IgG in myeloma cells is due to the presence of a relatively large quantity of translatable messenger RNA coding for IgG polypeptide chains, and that this messenger RNA is translated at a rate not significantly different from that of other cellular proteins.

3317 MYELOMA PROTEINS AS TUMOR-SPECIFIC ANTIGENS. (Eng.) Eisen, H. N. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, Mass.); Sakato, N.; Hall, S. J. *Transplant. Proc.* 7(2):209-214; 1975.

Evidence is summarized showing that immune responses to individually specific antigenic determinants (idiotypes) of a myeloma protein can specifically suppress growth of the tumor cells producing that protein. This indicates that myeloma proteins can function as tumor-specific antigens (TSAs). BALB/c mice can be stimulated to produce anti-idiotypic antibodies (ABs) to the respective idiotypes M315 and M460, which are immunoglobulin A (IgA) proteins produced by myeloma tumors MOPC-315 and MOPC-460, respectively. These ABs were detected by precipitation in a double Ab radioimmunoassay using ^{125}I-labeled myeloma protein, serum from BALB/c mice immunized with purified M315 or M460, and goat anti-mouse immunoglobulin. Transplanted MOPC-315 or MOPC-460 cells failed to form tumors in many BALB/c mice, due to an anti-idiotype response. The immunization was specific for the respective myeloma tumors. The resistance was particularly impressive with MOPC-315 because over half of the tumors which developed in specifically immunized mice turned out to be variants which, with one exception, secreted only the light chain (L^{315}). The variants remained stable during serial passage through unimmunized mice and thus appeared to arise not from antigenic modulation but from immunoselection of pre-existing variant cells. Myeloma proteins on the myeloma-cell surface were detected by virtue of the specific binding of 2,4,6-trinitrophenyl (Tnp) ligands by M315 and M460, whereby Tnp-RBC formed "direct" rosettes on MODC-315 and MOPC-460 cells. With hybrid Abs, formed from purified rabbit ABS to mouse α chains and from high affinity anti-Tnp ABS, more stable "indirect" rosettes were formed, but about 5% of the myeloma cells never formed rosettes in either the direct or indirect assay. When the lighter, nonrosetting MOPC-315 cells were removed from the heavier rosetting cells by centrifugation, they were found on inoculation into unimmunized BALB/c mice to give rise to variant tumors that produced only (L^{315}). Similar manipulation gave rise to a MOPC-460 variant. The rosette assay thus demonstrated the existence of rare variant cells in tumors that had been consistently passaged through unimmunized hosts. Further studies showed that 7 of 8 BALB/c myeloma proteins could successfully induce Ab responses in the same strain. One of the explanations that was offered was that most myeloma idiotypes are too rarely expressed to establish tolerance. With a radioimmunoassay employing goat Abs that were monospecific for different classes of mouse immunoglobulins, it was also found that most of the anti-idiotypes were immunoglobulin G1 (IgG1) and some were immunoglobulin G2a (IgG2a) molecules. It was proposed that determination of whether immunization with an anti-idiotype stimulates the production of its target idiotype or a completely different set of anti-anti-idiotype molecules would now be feasible.

3318 THE ISOLATION OF CARCINOEMBRYONIC ANTIGEN FROM TUMOR TISSUE AT NEUTRAL pH. (Eng.) Carrico, R. J. (Ames Res. Lab., Elkhart, Indiana 46514); Usategui-Gomez, M. *Cancer Res.* 35(11/Part 1):2928-2934; 1975.

Carcinoembryonic antigen (CEA) was purified from tumor tissue (liver metastases of human colonic carcinoma) under mild conditions at neutral pH by a procedure that utilized affinity chromatography on concanavalin A. Further purification by gel filtration provided CEA in 10-20% yield and 10% purity. Antibody to this preparation was rendered specific for CEA by adsorption on a column of normal liver proteins bound to Sepharose. On reaction by immunodiffusion against a crude tumor extract, the adsorbed antibody produced two precipitin lines, of which one was relatively weak. These two precipitin lines fused completely with the two respective lines produced by antibody to perchloric acid-treated CEA. The major antigen found in crude tumor extracts and in CEA preparations purified at neutral pH was nearly undetectable in perchloric acid extracts of tumor homogenates. Further investigations showed that 60-70% of the CEA in crude tumor extracts and in preparations isolated at neutral pH was destroyed and/or became insoluble under acidic conditions.

3319 CHEMOTHERAPEUTIC DRUGS INCREASE KILLING OF TUMOR CELLS BY ANTIBODY AND COMPLEMENT. (Eng.) Segerling, M. (Natl. Cancer Inst., Bethesda, Md.); Ohanian, S. H.; Borsos, T. *Science* 188(4): 55-57; 1975.

The *in vitro* effects of chemotherapeutic agents on the ability of xenogeneic antibody (antibody to Forssman antigen, anti-F) and guinea pig complement to kill tumor cells were investigated. Ascitic forms of diethylnitrosamine-induced guinea pig hepatoma cells (line-1 and line-10) were added to 5.0 ml of

tissue culture medium containing 50 μg/ml adriamycin, 20 μg/ml vincristine sulfate, 20 μg/ml azacytidine, 500 μg/ml 5-fluorouracil (5-FU), 500 μg/ml methotrexate (MTX), or 500 μg/ml 6-mercaptopurine (6-MP). Ascitic fluids were collected 8-10 days after ip injection of 3 x 10^6 tumor cells. Ascites tumor cells (60 x 10^6) were freed of RBC, washed twice with barbital-buffered saline and resuspended in culture medium. After incubation of 2.5 x 10^6 line-1 or line-10 cells for 17 hr at 37 C with one of the chemotherapeutic agents, 2.0 ml portions were washed and resuspended to a density of 10^6 cells/ml culture medium. Cell death was determined by staining cells with trypan blue after incubation with anti-F plus C. During this incubation, line-10 cells were more susceptible when they had been incubated with adriamycin (46% cell death), vincristine sulfate (50%), and azacytidine (69%) in comparison with controls (16%). Line-1 cells were more susceptible upon prior incubation with adriamycin (52% cell death), azacytidine (61%), 5-FU (69%), MTX (54%), and 6-MP (53%) when compared to controls (26%). The authors speculate that the beneficial effects of chemotherapeutic agents may be partially due to an increased susceptibility of tumor cells to antibody plus complement.

3320 CARCINOEMBRYONIC ANTIGEN: EVIDENCE FOR MULTIPLE ANTIGENIC DETERMINANTS AND ISOANTIGENS. (Eng.) Vrba, R. (Harvard Medical Sch., Boston, Mass. 02114); Alpert, E.; Isselbacher, K. J. *Proc. Natl. Acad. Sci. USA* 72(11):4602-4606; 1975.

Carcinoembryonic antigen (CEA) preparations were compared by radioimmunoassay. The preparations studied included four CEA standards (CEA-Roche, CEA-Montreal, CEA-City of Hope, and CEA-British) and CEA from serum and liver metastases of a patient with cancer of the colon who had an extremely high concentration of serum CEA (more than 26,000 ng/ml). The data indicate that the CEA-Roche standard differs significantly from the other three CEA standards tested, and that the serum CEA from the patient was antigenically different from currently available CEA standards as well as from the CEA obtained from the patient's own liver metastases. These antigenic differences were reflected in radioimmunoassay inhibition curves that were different and that were not affected by perchloric acid extraction of CEA. Because of the antigenic variation in the serum CEA, markedly different CEA concentrations (varying by three orders of magnitude) were measurable by two different antisera (Roche and Montreal). All the various CEA standards and samples cochromatographed on columns of Sepharose-6B, despite the large antigenic variation. It is claimed that CEA consists of a family of "isoantigens" with multiple antigenic determinants. A serum CEA isoantigen was identified that was different from currently available standards. Results of radioimmunoassays currently used for CEA measurement may not represent absolute concentrations of serum "CEA", but may reflect the binding affinity of different isoantigens to a particular polyvalent CEA antiserum.

3321 SUGGESTIVE EVIDENCE FOR *IN VIVO* BINDING OF SPECIFIC ANTITUMOR ANTIBODIES OF HUMAN MELANOMAS. (Eng.) Gupta, R. K. (Sch. Med. Univ. California, Los Angeles); Morton, D. L. *Cancer Res.* 35 (1):58-62; 1975.

A study was undertaken to determine whether or not antibodies could be eluted consistently from human malignant melanoma tissue obtained *via* biopsy or autopsy, and to determine the antitumor specificities of such antibodies. Tumor specimen suspensions were divided into five tubes and centrifuged at 2,500 rpm. The packed cells were treated as follows: cell in tube A were resuspended in nine volumes of 15% phosphate buffered saline solution; cells in tubes B, C, and D were resuspended in nine volumes of 15% NaCl solution and incubated at 4 C, 37 C and 56 C, respectively; and cells in tube E were resuspended in nine volumes of 0.56 M of glycine-HCl buffer. Eluted antibodies from five human melanomas reacted against melanoma antigens in a complement fixation test. Sonically treated homogenate showed no significant reaction against antibody serum before elution. Following elution, antigen activity increased (up to 32-fold). Eluate of one melanoma reacted with the sonically treated residue of other melanomas, but not with similarly prepared residues of sarcoma, carcinomas, or normal tissue. Melanoma eluates contained more immunoglobulin of Class G (IgG) than IgA. Traces of IgM were found in two melanoma eluates. Eluates in normal tissues (lung, kidney, and muscle) lacked serum proteins and showed no reaction with sonically treated melanoma residues. Thus, antibodies were consistently eluted from melanoma tissue and it appears that human malignant melanomas contain cell surface antigens which react with serum antitumor antibodies, *in vivo*.

3322 DEPRESSION OF THOMSEN-FRIEDENREICH (ANTI-T) ANTIBODY IN HUMANS WITH BREAST CARCINOMA. (Eng.) Springer, G. F. (Evanston Hosp., Northwestern Univ., Evanston, Ill. 60201); Desai, P. R. *Naturwissenschaften* 62(6):302-303; 1975.

Thomsen-Friedenreich (anti-T) antibody titers were determined in 189 patients with breast carcinoma, in 270 patients with benign breast disease (fibrocystic disease, fibroadenoma, or sclerosis), and in 740 noncarinomatous hospital controls. Patients who had been on oral antibiotics for over five days were excluded from the study. Forty of the breast carcinoma patients had an anti-T titer of 10 or less, compared with 14 of the patients with benign breast disease and with 17 of the noncarcinomatous controls. The difference in the anti-T titer between breast carcinoma patients and those with benign disease was significant ($P < 0.05$); when the breast cancer patients were compared with the controls, P was < 0.001. Titers of 12 or less were observed in 61 of the breast cancer patients, 22 of the patients with benign breast disease, and 39 of the controls. The P value was < 0.05 when breast cancer patients were compared with the benign breast disease group and < 0.02 when the cancer patients were compared with controls. Sixty-one patients with carcinomata other than those of the breast were also studied. Of these, nine had

an anti-T titer of 10 or less and 22 had a titer of 12 or less. When compared with the noncarcinomatous controls, P was < 0.02 for both titer scores of this small group. All individuals with severely depressed anti-T had normal serum IgG, IgA, and IgM values. Thus, the depressed activity may be due to binding of anti-T to breast cancer cell membranes and released cancer membrane antigens.

3323 ANTIBODY-INDUCED REDISTRIBUTION OF CEA ON THE CELL SURFACE: UTILIZATION IN SEPARATION OF CEA AND ISOANTIGEN A. (Eng.) Rosenthal, K. L. (Dept. Pathology, McMaster Univ., Hamilton, Ontario, Canada L8S 4J9); Palmer, J. L.; Harris, J. A.; Rawls, W. E.; Tompkins, W. A. F. *J. Immunol.* 115(4):1049-1053; 1975.

Antibodies specific for carcinoembryonic antigen (CEA) induced polar redistribution of CEA which was expressed on the surface of human intestinal carcinoma cells grown in tissue culture. Polar redistribution occurred at 23°C and 37°C but not at 4°C and was inhibited by sodium azide and cytochalasin B. Antibodies to isoantigen A did not react with CEA at the cell surface but did react with isoantigen A which was not redistributed by the antibody. Cells which expressed both CEA and isoantigen A were used to demonstrate that polar redistribution of CEA could be induced without altering the distribution of isoantigen A. The data indicate that CEA and isoantigen A can be expressed on the same cell as separate molecules.

3324 CARCINOEMBRYONIC ANTIGEN (CEA) AND RELATED ANTIGENS IN BLOOD CELLS AND HEMATOPOIETIC TISSUES. (Eng.) Bordes, M. (Lab. Experimental Medicine, INSERM U-45, Faculte de Medecine, Dijon, France); Knobel, S.; Martin, F. *Eur. J. Cancer* 11(11):783-786; 1975.

Indirect immunofluorescence was used to detect and localize carcinoembryonic antigen (CEA) and nonspecific cross-reacting antigen (NCA) in blood cells and hematopoietic tissues. Blood from 20 healthy donors, of various blood group status; and morphologically normal, sternal bone marrow samplings from five patients with mild anemia, of nonmalignant origin were used. The noncancerous specimens were two spleens, surgically removed after a traumatic rupture, two cervical lymph nodes (biopsies), with mild subacute lymphadenitis, and a morphologically normal lung. Peritoneal macrophages were obtained from the ascitic fluid of a patient with alcoholic cirrhosis of the liver. Three colonic noncancerous mucosa and their adjacent, noncancerous mucosa were also used. Nonspecific cross-reacting antigen was identified in the cytoplasm of blood polymorphonuclear cells, bone marrow myelocytes, and monocytic cells (probably macrophages) infiltrating the spleen and lymph nodes. In these tissues CEA was never found. In normal colon and colonic adenocarcinoma, CEA was present in the walls of epithelial cells, and in round, isolated polymorphonuclear or mononuclear cells, infiltrating the submucosa and the stroma of the tumor. The immunofluorescence staining of colon carcinoma by anti-NCA serum showed marked infiltration of the tumor stroma by polymorphonuclear and macrophagic cells.

3325 ISOLATION OF WILM'S TUMOR ANTIGENS BY CHELATION. (Eng.) Beierle, J. W. (Univ. Southern California Sch. Dentistry, Los Angeles, Calif. 90007); Wise, K. S.; Trump, G. N.; Allerton, S. E. *Clin. Chim. Acta* 61(3):411-414; 1975.

A procedure for EDTA extraction of minced Wilm's tumor was assessed as a method for isolating Wilm's tumor antigens. Extraction with 0.02% sodium-EDTA in phosphate-buffered saline was performed at room temperature for two hours with continuous stirring. The mixture was then centrifuged for 15 min at 20,000 x g, and the turbid supernatant (the "EDTA extract") was saved. A single precipitin line formed when rabbit antiserum, adsorbed with pooled human plasma and normal adult kidney EDTA homogenates, was allowed to react with the EDTA extract in Ouchterlony double diffusion tests. A line of complete indentity was observed between the EDTA tumor extract and EDTA extracts of *in vitro* cultures of Wilm's cells. Thus, the use of EDTA resulted in release of immunologically identical antigens from Wilm's tumor and a cultured Wilm's cell line. Chelation should therefore prove useful in isolating such membrane-bound antigens.

3326 INDUCTION OF EPSTEIN-BARR VIRUS-ASSOCIATED NUCLEAR ANTIGEN DURING *IN VITRO* TRANSFORMATION OF HUMAN LYMPHOID CELLS. (Eng.) Leibold, W. (Inst. Pathol., Hannover, East Germany); Flanagan, T. D.; Menezes, J.; Klein, G. *J. Natl. Cancer Inst.* 54 (1):65-68, 1975.

The induction of Epstein-Barr virus-associated nuclear antigen (EBNA) was studied in human lymphoid cells isolated from the peripheral blood of human adults (from cord blood), and from human fetal liver, spleen, bone marrow, and thymus. These were cultivated with or without a cell-free preparation of Epstein-Barr virus line B95-8 (EBV) that demonstrated transforming activity. In some cultures, phytohemagglutinin (PHA), concanavalin A (Con A), or pokeweed mitogen (PWM) were added in doses suboptimal with regard to DNA synthesis stimulation. Incubation was in RPMI-1640 medium, 36 C, 5% CO_2 in air, 80-95% relative humidity. All sera were checked to exclude the presence of antibody to nuclear antigen. A positive control consisted of a similarly prepared known EBNA-positive lymphoblastoid cell line (Raji). Uninfected test cells served as negative controls. The uninfected controls remained EBNA-negative. EBNA-positive lymphoblasts were first observed from days 1-6, mostly on day 3. This was followed by the appearance of some EBNA-positive small lymphoid cells. Transformation into permanent lymphoblastoid cell lines (LCL) was seen from days 12-19, at which point more than 80% of the cells were EBNA-positive. The results were similar in the mitogen-treated EBV-infected cultures, but mitogen alone did not produce EBNA-positive cells.

PHA produced a slightly lower percentage of EBNA-positive cells. Con A showed a longer latency period before EBNA-positive cells appeared, although transformation was observed after a normal latency. PWM caused an early appearance of EBNA-positive cells, the percentage of which was highest on day 2. With respect to the different groups of fetal cells, only the thymus specimens failed to show EBNA induction or establishment of LCL. The authors attribute the results of their mitogen study to the possibility that B-type lymphocytes have EBV receptors but T-type lymphocytes do not. PWM is known to affect both types, whereas PHA is a preferential mitogen for only the T-type. This was supported by the failure to induce EBNA or LCL in the fetal thymus cells. It is suggested that EBNA may be a necessary, although not in itself sufficient, condition for the growth of EBV-transformed lymphoid cells as permanent lines.

3327 A NEW MICROMETHOD FOR THE DETECTION OF HL-A ANTIGENS ON CULTURED HUMAN TUMOR CELLS. (Eng.) Fritze, D. (Harbor General Hosp., 1000 West Carson St., Torrance, Calif. 90509); Kern, D. H.; Drogemuller, C. R.; Pilch, Y. H.* *Transplantation* 20(3):211-218; 1975.

A rapid microcytotoxicity assay for the detection of HL-A antigens on tissue culture cells derived from human solid tumors is described. Tumor cells were prelabeled with ^{125}iododeoxyuridine. Isotopically labeled tumor cells were reacted with up to 37 highly selected HL-A antisera and diluted rabbit complement. Results of the HL-A typing of nine human tumor cell lines are reported. Three melanoma cell lines showed individually distinct HL-A profiles at the first HL-A locus which agreed with the antigenic pattern of the tumor donor's autologous lymphocytes. Less reactivity was noted with HL-A antisera defining second locus specificities on the three melanoma cell lines. Some other cell lines showed more HL-A reactions than were required to present a "full house." This method has obviated the necessity for visually enumerating residual tumor target cells.

3328 PURIFICATION OF POLYOMA T ANTIGEN FROM TRANSFORMED CELLS. (Eng.) Paulin, D. (Department de Biologie Moleculaire, Institut Pasteur, 75015 Paris, France); Gaudray, P.; Cuzin, F. *Biochem. Biophys. Res. Commun.* 65(4):1418-1426; 1975.

As a preliminary step toward analysis of the function of the polyoma virus gene, ts-a, at the biochemical level, a purification procedure was devised for T antigen, using complement fixation as an assay. Polyoma virus-transformed PY6 cells were radiolabeled, homogenized, and centrifuged 30 min at 30,000 *g*. The supernatant was treated with $(NH_4)_2SO_4$ to 20% saturation, the resulting precipitate was discarded, the new supernatant was 40% saturated with $(NH_4)_2SO_4$, and the precipitate obtained this time was redissolved in phosphate-buffered 10% glycerol and dialyzed against the same buffer. The preparation thus obtained was separated into two fractions, I and II, by chromatography on DEAE cellulose. The active fractions were further purified by selective removal of cell protein contaminants on immunoabsorbant columns made of Sepharose 4 B to which purified sheep antibodies to mouse cell protein were coupled. The fraction I now showed a purification factor of 356; the fraction II, a purification factor of 250. By electrophoretic analysis on SDS-polyacrylamide gels, using suitable reference standards, it was found that fraction II contained five main peptides with low background, while fraction I contained four main peptides and was more heterogeneous. The molecular weights (MW) of the main fraction II components were 52,000, 62,000, 68,000, 72,000 and 86,000; those of the fraction I components were 43,000, 60,000, 74,000 and 85,000. When the preparation obtained at the second $(NH_4)_2SO_4$ precipitation step was further purified by adsorptio on insolubilized anti-T antibodies and eluted with pH 2.2 glycine buffer, two components resolvable by polyacrylamide gel electrophoresis and showing MW of 70-75,000 and 80-90,000 were obtained. Two hypotheses were offered to explain the results. One was that the 70,000 MW peptide constituted the only viral gene product, while the 90,000 MW peptide was a cellular component associated with the viral protein. The other was that a mRNA corresponding to 70 80% of the early viral region was translated into the 90,000 MW peptide, which was, in turn, partially converted into a smaller antigenic component.

3329 BLOOD-GROUP PRECURSORS AND CANCER-RELATED ANTIGENS. (Eng.) Feizi, T. (Clinical Res. Center, Watford Road, Harrow, Middlesex HA1 3U7, England); Turberville, C.; Westwood, J. H. *an-Lancet* 2(7931):391-393; 1975.

Glycoprotein extracts from four primary colorectal carcinomas and from three liver metastases from colonic carcinomas were tested for blood-group precursor-like activities using human anti-I and anti-i cold agglutinins as reagents. Substantial activity was detected by quantitative precipitin assays in the high-molecular weight fractions of two metastatic tumors. A carcinoembryonic antigen (CEA) fraction from one of these tumors was also active. The CEA fraction with the highest precursor-like activity was incubated with the anti-I and anti-i sera; after centrifugation the supernatants and the washed precipitates were assayed for CEA activity. All the CEA activity was recovered in the supernatants, showing that the CEA and precursor-like activities are located on separate molecules. These data indicate that levels of precursor-like antigens in endodermal tumors and their possible diagnostic value warrant detailed investigation.

3330 MECHANISMS OF ACTION OF Ir GENES AND THEIR POSSIBLE APPLICATION TO TUMORS. (Eng.) Lonai, P. (Dept. Medicine, Univ. Stanford, Stanford, Calif.); Grumet, F. C. *Transplant. Proc.* 7(2):149-153; 1975.

To obtain evidence for the expression of *Ir* genes in T cells, an *in vitro* system was established to detect T-cell response to antigens which elicit im-

mune responses controlled by the *Ir-Ia* gene. Mice of strains C3H (H-2^k), CWB (H-2^b), C3H.Q (H-2^q), and B10.S (H-2^s) were immunized against the polypeptide antigens (T,G,)-A-L, (H,G)-A-L, or (Phe,G)-A-L, and the strains were classified as high or low responders on the basis of their *in vivo* antibody production. Lymph node lymphocytes from these animals were then tested for stimulation by antigen *in vitro* as determined by uptake of ^{3}H-thymidine. The results showed that lymphocytes from high responder animals were stimulated *in vitro*, while those from low responders were not. While anti-H-2 antisera inhibited the *in vitro* stimulation, anti-immunoglobulin sera that were inhibitory toward B-cell mitogens had no effect. This suggested that some components of the H-2 complex were involved in the *Ir* gene-regulated antigen-recognition by T cells. Since the region locating *Ir* genes was previously shown to contain at least two additional groups of loci, namely, *Lad*, and *Ia*, a study was carried out to obtain direct proof for the expression of different I-region genes on T cells. This was accomplished by the use of the mixed lymphocyte reaction for testing the response of purified lymph node T cells of certain mouse strains to stimulation by purified lymph node T and B cells of other mouse strains. The strains of mice were selected for stimulator or responder lymphocytes on the basis of differences in the *I*-region alone. The results suggested that all of three sub-regions of the *I*-region, namely, *Ir-Ia*, *Ir-Ib*, and *I-C* control antigens on both T and B lymphocytes. The exact genetic and functional relationship between *Ir* and *Lad* remains to be clarified. It was proposed that a more complete analysis of the function of *Ir* genes may contribute to a better understanding of the function of disease-susceptibility genes and the associated pathogenetic processes.

3331 GROWTH PROPERTIES AND ALLOANTIGENIC EXPRESSION OF MURINE LYMPHOBLASTOID CELL LINES. (Eng.) Zwerner, R. K. (Dept. Microbiology, Univ. Alabama in Birmingham Univ. Station, Birmingham, Ala. 35294); Acton, R. T. *J. Exp. Med.* 142(2): 378-390; 1975.

Murine lymphoblastoid cell lines were evaluated for their expression of Thy-1 and thymus leukemia (TL) differentiation alloantigens. Two culture conditions affected this expression. Cells grown in fetal bovine serum (FBS)-enriched medium expressed up to 15 times the amount of TL as cells grown in horse serum (HS)-enriched medium. Thy-1 expression was less affected by the type of serum used for culture. The phase of growth when the cells were harvested, was demonstrated to affect the expression of Thy-1. The expression of Thy-1.2 for one cell line examined, L-251A, during logarithmic growth was three-fold greater than cells collected during either lag or stationary growth. When culture conditions were standardized, a ranking of the amount of Thy-1 and TL expressed by several cell lines was made. All cell lines, except one, L-1210, expressed Thy-1. There was a 450-fold difference in the expression of Thy-1 between the cell lines evaluated. Seven cell lines expressed TL-1,2,3 with a ninefold difference in the amount of expression. The L-251A cell line was cultured in a 14 liter fermentor for a 26-day period. During this time TL and Thy-1 expression did not vary significantly, demonstrating that lymphoblastoid cell lines can be cultured on a continuous basis and will continue to express their surface alloantigens.

3332 GENERATION OF CYTOTOXIC T LYMPHOCYTES IN VITRO: V. RESPONSE OF NORMAL AND IMMUNE SPLEEN CELLS TO SUBCELLULAR ALLOANTIGENS. (Eng.) Engers, H. D. (Swiss Inst. Experimental Cancer Res., 1011 Lausanne, Switzerland); Thomas, K.; Cerottini, J.-C.; Brunner, K. T. *J. Immunol.* 115(2):356-360; 1975.

Subcellular particulate membrane fragments prepared from murine lymphoid or tumor cells were used as a cell-free antigen source in order to stimulate the generation of cytolytic thymus-derived effector cells (CTL) *in vitro*. Tumor cell lines syngeneic to C57BL/6 (EL4 leukemia), DBA/2 (P-815 mastocytoma, L-1210 lymphoma) and to BALB/c strains (MOPC-315 plasmocytoma) were maintained both in the ascitic form and *in vitro*. Cell-mediated cytotoxicity was determined by a ^{51}Cr release method. When cultivated with normal spleen cells as a source of responding lymphocytes, particulate antigen preparations induced only low CTL activities. However, normal responses were observed with spleens from C57BL/6 mice that had been made immune by inoculation with P-815 cells (30 x 10^6 cells, ip) 2-4 mo previously were used as a source of responding cells; cultures containing immune spleen cells showed a 3- to 5-fold higher lytic activity than primary cultures containing normal spleen cells when they were stimulated with irradiated DBA/2 spleen cells. In both cases, results were compared to those responses obtained with intact irradiated (1,000 rads) normal spleen cells as stimulating antigen. The effector cells generated with particulate antigen preparations (obtained either by hypotonic shock or by sonication) were shown to be T cells and were characterized with regard to the kinetics of their response and their dose-activity relationship. It was also shown that the responses observed were specific, both at the level of initiation and at the effector level. The results suggest that a fundamental difference exists between normal and alloimmune spleen cells in their ability to respond to stimulation by subcellular antigen preparations *in vitro*.

3333 LYMPHOCYTES IN PATIENTS WITH OVARIAN CANCER. (Eng.) Wolff, J. P. (Dept. Gynaecol., Gustave-Roussy Institute, Villejuif, France); De Oliveira, C. F. *Obstet. Gynecol.* 45(6):656-658; 1975.

The total number of circulating lymphocytes and their morphologic transformation in the presence of several antigens was studied. The subjects were 156 women, 81 of whom currently had an ovarian cancer or had had one in the past. Two control groups were used, including 54 normal women and 21 patients with malignancies other than ovarian cancer. Blood samples were taken and the total number of lymphocytes was determined. WBC suspensions were then incubated in

a medium containing phytohemagglutinin (PHA) or pokeweed mitogen (PWM). The number of lymphocytes transformed into lymphoblasts in the presence of the two antigens was then counted. There was a significant decrease in total lymphocytes in the pathologic control group and in the patients with ovarian cancer from the figures obtained in healthy women. In the presence of both antigens, lymphocyte transformation was significantly decreased from normal values in the pathologic control group and in patients who currently had an ovarian cancer. For the latter group, the survival at six months and the number of lymphocytes or the rate of transformation with phytohemagglutinin were correlated. The authors conclude that total lymphocytes in circulation and the rate of lymphoblastic transformation is a very important point in the prognosis for patients with ovarian cancer.

3334 B AND T CELL LYMPHOMAS: ANALYSIS OF BLOOD AND LYMPH NODES IN 87 PATIENTS. (Eng.) Gajl-Peczalska, K. J. (Box 609, University of Minnesota Hosp., Minneapolis, Minn. 55455); Bloomfield, C. D.; Coccia, P. F.; Sosin, H.; Brunning, R. D.; Kersey, J. H. *Am. J. Med.* 59(5):674-685; 1975.

B and T cell populations were studied in blood and neoplastic tissues from 64 untreated and 23 treated patients with non-Hodgkin's lymphoma. This study was undertaken to evaluate the relation of B and T cell markers in various lymphomas to the currently accepted morphologic classifications and to determine the utility of various tissues in defining the cell of origin of a lymphoma. When histologically involved blood, bone marrow, lymph nodes or body fluids were studied, a B or T cell origin of the lymphoma was identified in 68% of the patients. A B cell origin was found in 18% of adults classified as having nodular (N) or diffuse (D) poorly differentiated lymphocytic lymphoma (PDLL). One lymphoma of T cell origin was observed in an adult with poorly differentiated lymphocytic lymphoma-diffuse (PDLL-D). In contrast, all cases of PDLL-D in children were T cell in origin. The origin of American Burkitt's (stem cell) lymphoma in two children was the B cell. When histologically involved blood was studied, a B or T cell origin was demonstrated in 10 of 21 (48%) adults. Evidence of a monoclonal proliferation of B lymphocytes in the blood was found in two adults with more than 7 per cent lymphoma cells in Wright-Giemsa stained blood smears. When neoplastic lymph nodes were studied, the diagnosis of a B cell lymphoma was made in 8 of 12 (67%) adults. Study of surface markers on malignant cells in cerebrospinal or serosal fluids frequently revealed a B or T cell origin of the lymphoma. B and T lymphocyte numbers in the blood did not correlate with immunoglobulin or skin test abnormalities. Abnormalities in circulating B or T cell percentages at diagnosis were a poor prognostic sign in patients with PDLL-D.

3335 SEPARATION OF T LYMPHOCYTES FROM NORMAL INDIVIDUALS AND PATIENTS WITH B LYMPHOCYTE CHRONIC LYMPHOCYTIC LEUKAEMIA. (Eng.) Fernandez, L. A. (Camp Hill Hosp., Halifax, Canada); MacSween, J. M.; Langley, G. R. *Immunology* 28(2):231-241; 1975.

A technique is reported for obtaining a purified population of viable T lymphocytes from the peripheral blood of normal and leukemic subjects. Twenty-seven normal individuals and ten patients with chronic lymphocytic leukemia were studied. Identification of B cells was based on detection of membrane-bound immunoglobulins with the aid of fluorescein-conjugated antisera to human immunoglobulin determinants. T cells were identified by rosette-formation with SRBC. When lymphocytes collected from normal individuals and containing an average of 16.1% B cells were applied to IgG-anti-IgG-coated Degalan bead columns, held for two hours at 4 C, and eluted with medium 199, the eluted cells contained less than 2% B cells. When lymphocytes collected from leukemic patients and containing an average of 68.6% B cells were similarly fractionated, the eluted cells contained 36.4% B cells. To improve the purification of T lymphocytes from leukemic patients, columns of uncoated Degalan bead columns were first used to remove nonspecifically adherent cells. The lymphocytes eluted from this column were then applied to the IgG-anti-IgG-coated Degalan bead columns, and this resulted in a final preparation of T cells containing less than 2% B cells. For three cases of chronic lymphocytic leukemia with low density surface immunoglobulins, however, separation by this method was unsuccessful. Using a column prepared with Degalan beads coated with purified IgG which was previously heat-aggregated at 65 C for 45 min, then added to the beads and held at 37 C for 30 min, lymphocytes from a patient which had lost detectable surface immunoglobulins showed an increased proportion of rosette-forming T cells (from 4% before separation to 40% after separation).

3336 CYTOTOXICITY OF LYMPHOCYTES FROM HEALTHY SUBJECTS AND FROM MELANOMA PATIENTS AGAINST CULTURED MELANOMA CELLS. (Eng.) Pavie-Fischer, J. (Laboratoire d'Immunologie des Tumeurs, Institut de Recherches sur les Maladies du Sang, Centr Hayem, Hopital Saint Louis, 2, Place du Dr. Fournier, 75-010, Paris, France); Kourilsky, F. M.; Picard, F.; Banzet, P.; Puissant, A. *Clin. Exp. Immunol.* 21(3):430-441; 1975.

The *in vitro* cytotoxicity of lymphocytes from 47 melanoma patients (23 with primitive localized tumors and no detectable lymph node involvement; 24 with metastatic and recurrent tumors) and 13 healthy controls for cultured melanoma cells was studied in the ^{51}Cr release assay. Two different melanoma cell lines were used as target cells: SK Mel_1 cells cultured in suspension and NK l_1, a tissue culture line growing as a monolayer. Lymphocytes from most healthy subjects were cytotoxic to a variable extent for both cell lines; because of this variability, no correct control figure of a normal 'cytotoxic effect' could be defined. Approximately the same level of cytotoxicity was observed when lymphocytes from the same healthy subjects were retested after a 2-mo interval. A retrospective search for isoimmunization revealed previous transfusions and multiparity in three donors, but failed to explain the toxic effect of lymphocytes from the other subjects. Lymphocytes from the melanoma patients were also cytotoxic to the two melanoma cell lines, but the highest degree

of cytotoxicity was exhibited by lymphocytes from patients with primitive, localized tumors. It could not be excluded that different cytotoxic effects of lymphocytes from patients with primitive tumors and those with metastases were due to a nonspecific cytotoxicity of some mononuclear cells, more numerous in the peripheral blood at the onset of disease than in the dissemination stage.

3337 PHA STIMULATION OF SEPARATED HUMAN LYMPHOCYTE POPULATIONS. (Eng.) Potter, M. R. (Christie Hosp., Manchester M20 9BX, England); Moore, M. *Clin. Exp. Immunol.* 21(3):456-467; 1975.

Lymphocyte preparations from peripheral blood and tonsils were separated into populations enriched with T or B cells by formation of rosettes with SRBC and separation of the rosette-forming and non-rosette-forming populations. T cell-enriched populations were also prepared by nylon column filtration. Preparations were obtained which comprised 80-95% T or B lymphocytes as determined by E-rosette formation and surface immunoglobulin (Ig) staining. PHA responsiveness, measured by [^{3}H]thymidine incorporation, varied between relatively wide limits and was critically dependent on the degree of separation obtained. Relatively pure B-cell populations (<12% T cells) from blood and tonsils gave low PHA responses while preparations from blood still containing 24-38% T cells gave responses equal to or even greater than those of unseparated controls (60-78% T cells). T cell-enriched populations (80-86% T cells) responded to an equal or greater degree than controls, but more efficient separation (>90% T cells) resulted in markedly reduced stimulation. There was no simple correlation between the degree of phytomitogen-induced transformation and the number of T cells present. It is concluded that the low response of relatively pure T-cell populations may be due to depletion of B cells or non-lymphoid cells (or both) during the separation procedures. These observations have implications for the use of PHA stimulation as a measure of T-cell activity in mixed populations such as those of human peripheral blood leukocytes.

3338 DIFFERENTIATION OF LYMPHOID CELLS OF THE B CELL SERIES ACCORDING TO MEMBRANE AND CYTOPLASMIC DETERMINANTS. (Eng.) Knapp, W. (Institut for Immunologie der Universitat Wien, B Borschkegasse 8 a, Austria); Baumgartner, G.; Holowiecki, J. *Acta Neuropathol. Suppl. (Berlin)* 6:37-40; 1975.

Previous investigations have shown that a large proportion of normal human lymphocytes bearing membrane IgM also have independently moving IgD molecules on their surface. Since the majority of patients with chronic lymphatic leukemia (CLL) are also known to have high numbers of lymphocytes with detectable membrane IgM, CLL cells were investigated for the presence of membrane IgD by a fluorescence staining technique. In the 18 patients studied, the sum of the percentages of cells with surface IgM (mean 90.06%) and IgD (mean 83.6%) exceeded the percentage of cells stained for total immunoglobulin (mean 91.1%). That a high proportion of lymphocytes carried IgM as well as IgD on the surface suggests that the differentiation of these cells might be blocked at the step where IgD and IgM overlap, with IgD disappearing as soon as the cells start to secrete IgM. The lymphocytes of the CLL patients were therefore investigated for crystalline immunoglobulin inclusions. In none of the 18 cases could the inclusions be found. Further investigation of the two immunoglobulin receptors in malignant lymphocyte proliferations might give a better understanding of the underlying mechanisms.

3339 EFFECTS OF MITOGENS FOR MOUSE B LYMPHOCYTES ON CHICKEN LYMPHOID CELLS. (Eng.) Tufveson, G. (Biomedical Center, Box 571, S-751 23 Uppsala, Sweden); Alm, G. V. *Immunology* 29(4): 697-707; 1975.

Because *Escherichia coli* lipopolysaccharide (LPS), tuberculin-purified protein derivative (PPD), and dextran sulfate (DxS) were known to be potent mitogens for mouse B lymphocytes and to enhance polyclonal antibody synthesis in mouse spleen cells, a study of the effects of these mitogens and also of the T-cell mitogen, concanavalin A (Con A), on chicken lymphoid cells was carried out for comparison. The effect of bursectomy on the mitogen-induced proliferative response of chicken spleen cells was also studied. The chickens were White Leghorn Babcock B-300 strain; control mice were CBA/J strain. Chemical bursectomy in the chickens was performed by ip injection of cyclophosphamide. Cultures of chicken spleen, thymus, and bursa cells and of mouse spleen cells were prepared in RPMI 1640 medium. [^{3}H]-thymidine uptake was used as an indicator of mitogen stimulation of cell proliferation. Tests for polyclonal antibody synthesis were based on the occurrence of plaque-forming cells (PFC) in unimmunized cultures, using a method involving SRBC and TNP-coupled SRBC as target cells. Tests for primary antibody response were carried out by immunizing cultures with SRBC *in vitro* and subsequently assaying the cultures for direct PFC using SRBC as target cells. LPS and PPD increased the proliferation of chicken spleen cells in culture, but DxS was not stimulatory. Thymus and bursa lymphocytes were not stimulated by any of these compounds. Spleen cells from bursectomized chickens showed decreased responses to LPS and PPD, but responded normally to the T-cell mitogen Con A. None of the tested mitogens induced polyclonal antibody synthesis or directly enhanced the primary antibody response to SRBC in spleen cell cultures. LPS-coated SRBC, however, enhanced the *in vitro* antibody response to SRBC. The results suggested a moderate proliferative response of chicken lymphocytes to LPS and PPD, possibly involving B cells, but no further effects comparable to those observed with mouse B lymphocytes.

3340 BLOCKING OF SPLEEN CELL ACTIVITY AGAINST TARGET MAMMARY TUMOR CELLS BY VIRAL ANTIGENS. (Eng.) Blair, P. B. (Dept. of Bacteriology, Univ. of California, Berkeley, Calif. 94720); Lane, M. A.; Yagi, M. J. *J. Immunol.* 115(1):190-194; 1975.

A series of microcytotoxicity tests were used to

answer the questions of whether antigen alone is sufficient to inhibit spleen cell activity, and whether antigens of the mammary tumor virus (MTV) are effective in blocking spleen cell activity against mammary tumor cells. Virus preparations derived from the milk of six strains of mice and from culture fluids of the FUKU cell line were the source of antigen. Spleen cells from three types of donors were sources of immune cells. Cultures of MTV-induced BALB/cfC3H mammary tumors and a non-MTV-producing FUKU cell line served as sources of target cells. The donors consisted of two adult virgin BALB/cfC3H females, which made a T cell response to the tumor antigen; four multiparous but tumor-free BALB/cfC3H females, which made an even stronger T cell response, and a non-T cell response; and one adult virgin BALB/c female, whose response was entirely non-T cell. Three procedures were used for testing for blocking activity: (1) the target cells were treated with the antigen, (2) virus and spleen cells were added to target cells at the same time, and (3) the spleen cells were incubated with the antigen for 30 min before addition to the target cells. No blocking was observed by the first procedure; it was strongest by the third procedure. The T cell responses of the virgin and multiparous BALB/cfC3H females were effectively blocked, while non-T responses of multiparous BALB/cfC3H tumor-free females or of virgin BALB/c females were blocked by some, but not all, of the MTV antigen preparations. Murine leukemia virus (MuLV) was ineffective in blocking spleen cell activity against the MTV-induced mammary tumor cells. In comparable experiments involving the use of MuLV as the antigen, MuLV-producing FUKU cells as the target cells, and FUKU-sensitized lines as sources of spleen cells, the MuLV antigen was effective as a blocking agent, while MTV was not. The specificity of blocking demonstrates that it is immunologic in nature.

3341 RESISTANCE TO HERPES SIMPLEX TYPE 2 VIRUS INDUCED BY AN IMMUNOPOTENTIATOR (PYRAN) IN IMMUNOSUPPRESSED MICE. (Eng.) Morahan, P. S. (Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, Va. 23298); McCord, R. S. *J. Immunol.* 115(1):311-313; 1975.

The protective effects of pyran, an interferon inducer and immunopotentiator, against herpes simplex virus type 2 (HSV-2) were investigated in normal female BALB/c mice and in mice depleted of thymus-derived (T) lymphocytes by thymectomy, lethal irradiation (900 R), and bone marrow reconstitution (TXB mice). Adult (16-wk-old) TXB mice were approximately ten times more susceptible than agematched normal mice to iv or intravaginal infection with HSV-2. The LD_{50} for iv HSV-2 in normal adult mice was $10^{3.5}$ plaque-forming units (PFU) compared with $10^{2.4}$ PFU in adult TBX mice. However, 5-wk-old mice were even more susceptible to HSV-2 than were adult TBX mice ($LD_{50}=10^{1.4}$), indicating that factors other than T cells are involved in resistance to HSV-2. Pyran treatment (25 mg/kg, iv) significantly prolonged the mean survival time and reduced the mortality of both normal and TXCB mice infected iv with challenge doses of viruses ranging over 1,000-fold in concentrations. The LD_{50} increased to $10^{3.6}$ PFU in TBX mice and to $10^{4.1}$ PFU in normal mice. Treatment of TXB mice with pyran before intravaginal infection with HSV-2 (10^5 PFU) was also effective in significantly prolonging the mean survival time, although the drug was not as effective against intravaginal HSV-2 as against iv HSV-2. These results suggest a possible role for immunopotentiator-activated macrophages in the increased resistance afforded to mice by pyran treatment. As previously shown, the pyran-induced activation of macrophages is apparently independent of T cells because the drug induced the production of macrophages cytotoxic for tumor cells in TXB mice.

3342 *IN VITRO* LYMPHOCYTE REACTIVITY AND T-CELL LEVELS IN CHRONIC CIGARETTE SMOKERS. (Eng.) Silverman, N. A. (Natl. Cancer Inst., Bethesda, Md. 20014); Potvin, C.; Alexander, J. C., Jr.; Chretien*, P. B. *Clin. Exp. Immunol.* 22(2): 285-292; 1975.

Peripheral blood total WBC, lymphocyte and thymus-dependent lymphocyte (T cell) levels and *in vitro* lymphocyte reactivity (LR) to phytohemagglutinin (PHA) were determined in 153 chronic cigarette smokers (58 men, 95 women, 20-78 yr old, mean 35 yr) and 115 nonsmokers (51 men, 64 women who had smoked; 20-78 yr old, mean 37.6 yr). In nonsmokers the WBC, lymphocytes, and T cells/mm^3 were 6023, 1981, and 1382, respectively. In smokers the corresponding levels were 6803, 2325, and 1594, respectively. The WBC levels for smokers with 3-10 pack-yr (packs/day x years of smoking) was 6417, and for more than 50 pack/yr, 7662/mm^3. The WBC level in nonsmokers over 50 yr old was 6411/mm^3. There was no correlation of lymphocyte or T cell levels with age. Lymphocyte reactivity to PHA was significantly higher in smokers less than 40 yr of age or in those with a 20 pack-yr usage level. Older smokers or those with a history of heavier cigarette consumption did not differ from normals in LR to PHA, contrary to previous reports. The elevated WBC levels in smokers may be secondary to chronic subclinical pulmonary inflammation. The selection of older smokers may have been biased by the exclusion of those not in good health.

3343 THE Fc RECEPTOR ON THYMUS-DERIVED LYMPHOCYTES: II. MITOGEN RESPONSIVENESS OF T LYMPHOCYTES BEARING THE Fc RECEPTOR. (Eng.) Stout, R. D. (Stanford Univ. Sch. Medicine, Stanford, Calif. 94305); Herzenberg, L. A. *J. Exp. Med.* 142(5):1041-1051; 1975.

The responsiveness of purified Fc^- and Fc^+ thymus-derived (T) lymphocytes, isolated from normal BALB/cN mouse spleen cell populations by cell sorting on the fluorescence activated cell sorter, was examined. Although both Fc^- and Fc^+ T cells responded to phytohemagglutinin (2.5 μg/ml,) 48 hr, the response to concanavalin A (Con A 1.5 μg/ml, 48 hr) was found to be a characteristic of the Fc^+ T lymphocyte. The poor responsiveness of the Fc^- T cells to Con A was shown not to be due to a requirement for either different concentrations of Con A (0.15-5.0 μg/ml Con A, 0.5-5.0 μg/ml phytohemagglutinin) or for adherent cells. The addition of Fc^+ T cells to the Fc^- T cells in a ratio of 1:3 resulted in a mitotic re-

sponse not significantly different from that observed with the purified Fc^+ T cells alone and up to 15-fold greater than that of Fc^- T cells alone. It is suggested that the Fc^- T cells can be recruited into mitosis as a result of Con A stimulation of the Fc^+ T cells.

3344 THE SEZARY SYNDROME CELL: SURFACE ULTRASTRUCTURAL CHARACTERISTICS. (Eng.) Golomb, H. M. (Univ. Chicago Hospitals, 950 East 59th St., Chicago, Ill. 60637); Braylan, R.; Reese, C.; Variakojis, D.; Brynes, R. K.; Yachnin, S. *Acta Haematol. (Basel)* 54(2):106-114; 1975.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were used on three different occasions to determine the surface ultrastructural characteristics of peripheral blood mononuclear cells from a 60-yr-old woman with Sezary syndrome. Prior immunofluorescence studies on four occasions had shown that the cells lacked surface immunoglobulins and ability to form E-rosettes, and had a markedly depressed response to mitogens. Cells examined by TEM within a 2-mo interval had the characteristic highly convoluted nuclei; no projections were seen in the cytoplasmic borders. Four months later, most of the cells observed by TEM had a smooth spherical surface, and microvilli were rare. Two studies by SEM the following month showed that most cells were spherical with moderate numbers of microvilli. On the last occasion a simultaneous SEM study also demonstrated moderate numbers of microvillous projects in the cytoplasmic borders. The similarity of surface projections revealed by both SEM and TEM in the same sample suggests that the methods can be freely interchanged when cytoplasmic projections are analyzed. The SEM technique allows depth-of-field viewing of a cell hemisurface, while the TEM method enables an exact correlation of nuclear and characteristics with surface projections. Because the smooth surface on a spherical cell is known to be consistent with a T lymphocyte origin, the authors suggest that the Sezary syndrome in this patient may be related to a T lymphocyte that has lost certain surface markers and mitogen response characteristics through a process of dedifferentiation.

3345 FAILURE OF PERITONEAL EXUDATE MACROPHAGES TO REVERSE IMMUNOLOGIC IMPAIRMENT BY FRIEND LEUKEMIA VIRUS. (Eng.) Ceglowski, W. S. (Departments Microbiology, Pennsylvania State Univ., Univ. Park, Pa.); Friedman, H. *Proc. Soc. Exp. Biol. Med.* 148(3):808-812; 1975.

Since adoptively transferred normal lymphocytes had been found to be effective in restoring immunocompetence to leukemia virus-infected animals, it was of interest to determine whether adoptively transferred normal macrophages might be similarly effective. The test animals were Balb/c mice, inoculated ip with Friend leukemia virus. Peritoneal exudate (PE) cells, used as the source of macrophages, were obtained from Balb/c mice 24 hr after ip inoculation with incomplete Freund's adjuvant. For cell transfer, 1 or 3 x 10^7 PE cells were injected ip or iv into recipient Balb/c mice 18-24 hr before challenge immunization with 0.5 ml of 0.5-5.0% sheep RBC. Immunocompetence was assessed by measurement of spleen cell antibody formation in a plaque assay, as determined by localized hemolysis in a suspension of spleen cells and sheep RBC in agar gel. It was found that transfer of macrophages from normal mice to leukemia virus-infected recipients had no effect on the virus-induced impairment of the immune response. Similar transfer of macrophages to normal uninfected mice generally resulted in a moderate depression of the expected immune response. In no case, however, did the macrophages enhance the immune responses in normal or virus-infected mice. It appeared likely that the defect in immunocompetence of the leukemic mice lay mainly with impairment of antibody forming cells and their precursors and not with antigen processing cells *per se*.

3346 METHODOLOGICAL APPROACHES TO THE STUDY OF CARBOHYDRATE SURFACE RECEPTORS ON MACROPHAGES AND TUMOR CELLS. (Eng.) Wollweber, L. (Inst. Microbiology and Experimental Therapy, 69 Jena, German Democratic Republic); Fritsch, S. *Neoplasma* 22(2):157-162; 1975.

Specific carbohydrate receptors on cells were shown to be made visible by ultracytochemical methods using concanavalin A (Con A), followed by peroxidase (PO); Con A precoupled with PO; *Ricinum communis* agglutinin precoupled with PO; or wheat germ agglutinin, followed by ovomucoid precoupled to PO. Precoupling was accomplished with the aid of glutaraldehyde (GA). The catalytic activity of the PO was revealed in each case by final treatment of the cells with diaminobenzene and osmium tetroxide. The rationale behind the use of the different combinations was based on the specificity of the carbohydrate receptors involved. The cells used in the tests were macrophages originating from peritoneal cells of AB/Jena mice and tumor cells originating from L1210 ascites tumors of $NMDF_1$ mice. The reactions were carried out on native cells, suspended in phosphate-buffered saline, and also on GA-fixed cells in 2% GS-cacodylate buffer. Lectin-treatment of native cells resulted in agglutination, while lectin-treatment of GA-fixed cells did not. A relatively continuous dark surface layer of variable thickness could be demonstrated on GA-fixed cells, while native cells showed a discontinuous surface coat characterized by strongly marked and almost contrastless membrane segments. Quantitative estimations of the Con A reaction products were based on two parameters: area per length of membrane (A/L), as a parameter for the thickness of the reaction product; and frequency of features (N/L), as a parameter for the discontinuity of the surface reaction. A/L and N/L were inversely proportional, indicating that the thicker the surface reaction, the rarer its interruptions. Native macrophages showed greater variations of thickness of stained cell coat from one segment to another than did GA-fixed macrophages. Different individual peritoneal cells showed uniform mean values for A/L over the total circumference, indicating a lack of loss of glycocalyx of native normal peritoneal cells during the preparation process, as had previously been found for certain tumor cells.

3347 INHIBITION OF THE CELLULAR IMMUNE RESPONSE TO SIMIAN VIRUS 40 TUMOR CELLS IN TUMOR-BEARING TUMOR-IMMUNE MICE BY CONCANAVALIN A. (Eng.) Davis, S. (Public Health Serv., U.S. Dep. Health, Educ. Welfare, Bethesda, Md.); Boone, C. W. *J. Natl Natl. Cancer Inst.* 54(2):435-438; 1975.

The effects of *in vivo* administration of concanavalin A (Con A) on the primary and secondary immune responses of male BALB/cAnN mice to syngeneic simian virus 40 (SV40)-induced tumor cells (E4) were investigated. To demonstrate the effects of Con A on established tumor immunity, 10^6 E4 tumor cells were injected into the foot pads of immunized mice at different times (day 0, 1-5, 9, 11) after *in vivo* administration of the Con A. The mice were immunized by excision of growing tumors ten days after inoculation with 10^6 E4 cells. One group of E4-immune mice received a single ip injection of 400 μg Con A on day 0; another group received 50 μg Con A daily from day 0. The single dose of Con A immediately and markedly suppressed the immune response, which slowly returned to normal levels in six days. The small, continuous doses given daily caused a gradual decrease, which tended to reach a plateau by the fifth day. To determine the effects of Con A on the cell-mediated immune response in mice with progressively growing tumors, the radioisotopic foot-pad assay was used on mice at various intervals (days 0, 2, 6, 8, 12, and 16) after implantation of E4 cells in the foot pad. When the single dose of Con A was used, the response was significantly depressed, and the depression was greatest on the eighth day; when the daily dose regimen was used, the depression on the eighth day was still greater. When the tumors were excised on day 25, those from the Con A-treated mice were significantly greater in size than those of the untreated control mice. These results showed that Con A suppressed cellular response to progressively growing tumor and enhanced tumor growth. To determine the effect of spleen cells from Con A-treated E4-immune mice on the local adoptive transfer of E4 immunity, E4-immune mice were given ip injections of 400 μg Con A; 16 hr later, the spleen cells were removed and single cell suspensions were prepared. Then 20 x 10^6 spleen lymphocytes were mixed with 10^6 E4 tumor cells and injected into the foot pads of treated immune control mice. The reversibility of this immunosuppression was shown by near total restoration of immune reactivity after incubation of the lymphocytes with α-methyl-D-pyranosyl sugars. This suggests that the mechanism by which Con A suppresses cell immune reponse may be due, in part, to its ability to bind to receptors on T cell membranes.

3348 LYMPHOCYTE-MEDIATED CYTOTOXICITY AGAINST TUMOR CELLS. I. CON A ACTIVATED CYTOTOXIC EFFECTOR CELLS EXHIBIT IMMUNOLOGICAL SPECIFICITY. (Eng.) Waterfield, J. D. (Division of Immunology, Karolinska Institutet, Wallenberger-laboratory, Lilla Freskati, 104 05 Stockholm 50, Sweden); Waterfield, E. M.; Moller, G. *Cell. Immunol.* 17(2):392-404; 1975.

The phenonenon of concanavalin A (Con A)-induced cytotoxicity in spleen cells of mice was analyzed with regard to similarities between *in vivo* and *in vitro* cytotoxic activation. The cells were observed for the expression of Con A-induced cytotoxicity when Con A was present or absent in the assay system. A/Sn (H-2^a), A/Sn x B10 5M (H-$2^{a/b}$), B10 5M (H-2^b), CBA (H-2^k), C57 Leaden (H-2^b), and DBA/2J (H-2^d) mice, both age and sex matched, were used. For maximum *in vivo* activation, 240 μg Con A in 0.1 ml injected iv was used routinely. To establish dose-response curves, mice were similarly injected with 6-480 μg Con A. The tumors used as sources of target cells were the YAC Molony virus-induced ascites leukemia (H-2^a) and the DBA/2J P815 (H-2^d). The target cells were labeled with 5-iodo-2-deoxyuridine-I^{125} (^{125}IUdR). Spleen cells from Con A-injected mice were cytotoxic to allogeneic tumor target cells *in vitro*, the degree of cytotoxicity being dependent upon the dose of Con A. Cytotoxicity did not occur when the lymphocytes were syngeneic to the target cells. When extraneous Con A was added to the mixture of syngeneic lymphocytes and target cells, cytotoxicity occurred to the same extent as that found in allogeneic combinations without the addition of Con A. Analogous findings were observed when spleen cells were activated with Con A *in vitro*. Only allogeneic lymphocytes caused cytotoxicity after treatment with the competitive ligand, methyl-*α*, D-mannopyranoside to remove surface bound Con A. However, extraneously added Con A also caused expression of cytotoxicity with syngeneic Con A-activated lymphocytes. It is concluded that Con A transforms lymphocytes into cytotoxic effector cells, but that these cells cannot express cytotoxcity unless they bind to the target cells. The author suggests that allogeneic Con A-activated lymphocytes recognize the target cells by clonally distributed recognition receptors and are therefore capable of binding to the targets by themselves. Syngeneic cells, on the other hand, do not possess such receptors, and consequently can only express cytotoxicity when agglutinated to the targets by extraneous agents such as Con A.

3349 A COMPARATIVE STUDY OF FOUR CYTOCHEMICAL DETECTION METHODS OF CONCANAVALIN A BINDING SITES ON THE CELL MEMBRANE. (Eng.) Temmink, J. H. M. (Netherlands Cancer Inst., Amsterdam, Netherlands); Collard, J. G.; Spits, H.; Roos, E. *Exp. Cell Res.* 92(2):307-322; 1975.

Four different electron cytochemical methods to detect concanavalin A (ConA) binding sites on the plasma membrane of mouse fibroblasts were compared. The ConA binding sites were made visible either by adding ConA, followed by horseradish peroxidase (HRP) or hemocyanin (HC), or by marking the sites with complexes of ConA with ferritin (Fer) or with microperoxidase (MP). HC and Fer were directly visible in the electron microscope; HRP and MP were detected by their electron-dense reaction production with diaminobenzidin and H_2O_2. Differences in sensitivity of the ConA binding sites for the different markers were found and resulted in a tentative interpretation of the labeling reactions. All experiments suggested that normal and transformed murine fibroblasts both have plasma membranes in which

the binding sites can move equally well and can be induced to form clusters. The results have made it possible to confirm the existence of clustering of ConA binding sites in the membrane, and to show that differences in clustering between cells are not a sufficient cause for differences in agglutinability of these cells.

3350 STIMULATION OF SPECIFIC IMMUNITY AGAINST CANCER BY NEURAMINIDASE-TREATED TUMOR CELLS. (Eng.) Bekesi, J. G. (Mount Sinai Sch. Medicine and Hosp., City Univ. New York, New York, N.Y.). *Prog. Clin. Biol. Res.* 4:65-67; 1975.

3351 HUMORAL IMMUNOSTIMULATION. IV. ROLE OF COMPLEMENT. (Eng.) Shearer, W. T. (Washington Univ. Sch. Med., St. Louis, Mo.); Atkinson, J. P.; Frank, M. M.; Parker, C. W. *J. Exp. Med.* 141(4):736-752; 1975.

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3354 COMPARISON OF THE IMMUNOGENICITY OF HAMSTER CELLS TRANSFORMED BY ADENOVIRUS AND HERPES SIMPLEX VIRUS. (Eng.) Thiry, L. (Institut Pasteur du Brabant, Province de Brabant, 1040 Brussels, Belgium); Sprecher-Goldberger, S.; Tack, L.; Jacques, M.; Stienon, J. *Cancer Res.* 35(4): 1022-1029; 1975.

3355 MECHANISM OF INDUCTION OF CELL-MEDIATED IMMUNITY TO VIRUS INFECTIONS: *IN VITRO* INHIBITION OF INTRACELLULAR MULTIPLICATION OF MOUSE ADENOVIRUS BY IMMUNE SPLEEN CELLS. (Eng.) Hamada, C. (Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan); Uetake, H. *Infect. Immun.* 11(5):937-943; 1975.

3356 CELL-MEDIATED IMMUNITY TO MOLONEY SARCOMA VIRUS IN MICE. II. ANALYSIS OF ANTIGENIC SPECIFICITIES INVOLVED IN T LYMPHOCYTE-MEDIATED *IN VIVO* REJECTION OF MURINE SARCOMA VIRUS-INDUCED TUMORS. (Eng.) Gorczynski, R. M. (Dep. Zool., Univ. Coll., London, England); Knight, R. A. *Eur. J. Immunol.* 5(2):148-155; 1975.

3357 MELANOMA ANTIGENS THAT PRODUCE CELL-MEDIATED IMMUNE RESPONSES IN MELANOMA PATIENTS: JOINT U.S.-U.S.S.R. STUDY. (Eng.) Gorodilova, V. V. (Hertsen Scientific Res. Oncology Inst., Moscow, U.S.S.R.); Hollinshead, A. *Science* 190(4212):391-392; 1975.

3358 A STUDY OF IMMUNE-SUPPRESSIVE ACTIVITY OF HERPES SIMPLEX VIRUS TYPE 2 AND THE TUMOR ENHANCING POTENTIAL OF THE VIRUS ON YOSHIDA SARCOMA. (Eng.) Reiss-Gutfreund, R. J. (Institut fur Krebsforschung, Universitat Wien, Austria); Dostal, V. *Osterr. Z. Onkol.* 2(2/3):63-68; 1975.

3359 IMMUNOSUPPRESSIVE EFFECT OF A HUMAN HEPATIC GLYCOFERROPROTEIN, α2H GLOBULIN: A STUDY ON THE TRANSFORMATION OF NORMAL HUMAN LYMPHOCYTES. (Eng.) Buffe, D. (Inst. de Recherches Scientifiques sur le Cancer, 94 Villejuif, B. P. No. 8, France); Rimbaut, C. *Immunology* 29(1):175-184; 1975.

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3366 AUTOANTIBODIES WITH ANTILIPOPROTEIN SPECIFICITY AND HYPOLIPOPROTEINEMIA IN PATIENTS WITH CANCER. (Eng.) Riesen, W. (Inst. Clin. Exp. Cancer Res. Univ. Berne, Tiefenau-Hosp., Switzerland land); Noseda, G.; Morell, A.; Bütler, R.; Barandun, S.; Nydegger, U. E. *Cancer Res.* 35(3):535-541; 1975.

3367 IMMUNE COMPLEXES ASSOCIATED WITH NEOPLASIA: PRESENCE OF EPSTEIN-BARR VIRUS ANTIGEN-ANTIBODY COMPLEXES IN BURKITT'S LYMPHOMA. (Eng.) Oldstone, M. B. A. (Scripps Clinic and Res. Foundation, La Jolla, Calif.); Theofilopoulos, A. N.; Gunven, P.; Klein, G. *Intervirology* 4(5):292-302; 1974.

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S.; Greaves, M. F.; Hogg, N.; Boylston, A. *Ann. N.Y. Acad. Sci.* 249:424-437; 1975.

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3385 HUMAN LYMPHOCYTE SURFACE IMMUNOGLOBULIN CAPPING. NORMAL CHARACTERISTICS AND ANOMALOUS BEHAVIOR OF CHRONIC LYMPHOCYTIC LEUKEMIC LYMPHOCYTES. (Eng.) Cohen, H. J. (Veterans Adm. Hosp., Durham, N.C.); Gilbertsen, B. B. *J. Clin. Invest.* 55(1):84-93; 1975.

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3390 "NATURAL" KILLER CELLS IN THE MOUSE. I. CYTOTOXIC CELLS WITH SPECIFICITY FOR MOUSE MOLONEY LEUKEMIA CELLS. SPECIFICITY AND DISTRIBUTION ACCORDING TO GENOTYPE. (Eng.) Kiessling, R. (Karolinska Inst., Stockholm, Sweden); Klein, E.; Wigzell, H. *Eur. J. Immunol.* 5(2):112-117; 1975.

3391 "NATURAL" KILLER CELLS IN THE MOUSE. II. CYTOTOXIC CELLS WITH SPECIFICITY FOR MOUSE MOLONEY LEUKEMIA CELLS. CHARACTERISTICS OF THE KILLER CELL. (Eng.) Kiessling, R. (Karolinska Inst., Stockholm, Sweden); Klein, E.; Pross, H.; Wigzell, H. *Eur. J. Immunol.* 5(2):117-121; 1975.

3392 IDENTIFICATION OF MACROPHAGE-LIKE CHARACTERISTICS IN A CULTURED MURINE TUMOR LINE. (Eng.) Koren, H. S. (Natl. Cancer Inst., Bethesda, Md.); Handwerger, B. S.; Wunderlich, J. R. *J. Immunol.* 114(2/Part 2):894-897; 1975.

3393 INTERACTION OF *LENS CULINARIS* LECTIN, CONCANAVALIN A, *RICINUS COMMUNIS* AGGLUTININ AND WHEAT GERM AGGLUTININ WITH THE CELL SURFACE OF NORMAL AND TRANSFORMED RAT LIVER CELLS. (Eng.) Roth, J. (Inst. Pathology, Friedrich-Schiller-Univ., DDR--69 Jena, Ziegelmuhlenweg 1, East Germany); Neupert, G.; Thoss, K. *Exp. Pathol. (Jena)* 10(5/6): 309-317; 1975.

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See also:

* (Rev): 3004, 3055, 3056, 3057, 3058, 3059, 3060, 3061
* (Chem): 3105, 3123, 3140
* (Phys): 3181
* (Viral): 3208, 3211, 3226, 3255, 3266, 3271, 3272, 3290, 3292
* (Path): 3406, 3407, 3418, 3422, 3425, 3447, 3450, 3481

3396 HYPERPLASIA OF RAT MAMMARY GLAND *IN VITRO*. (Eng.) Palekar, L. (New York Univ. Med. Cent., N.Y.): Waldo, E. D.; Seidman, I. *J. Natl. Cancer Inst.* 54(1):235-240; 1975.

Tests were carried out to determine if the intraductal hyperplasia of rat mammary explants in the presence of insulin is caused by proliferation of epithelial or of myoepithelial cells, or if sex hormones affect the process. Mammary explants were cultured at 37 C, 90% O_2, and 10% CO_2, with 5 µg/ml Sigma bovine insulin and routine additions of penicillin (100 U/ml) and streptomycin (100 µg/ml). The cultures were terminated at 1, 2, 3, and 4 wk, with maximum hyperplasia occurring at about two weeks. The hyperplasia exhibited trabecular, papillary, and, rarely, concentric morphologic patterns. Electron microscopic examination of 20 explants for each time period showed the proliferating cell to be epithelial, not myoepithelial. Estrogen at 0.01 µg/ml showed no inhibitory effect on insulin-induced hyperplasia, thus contradicting previous reports; testosterone at 6 µg/ml inhibited the hyperplasia by about half, but only when it was added at the beginning of the culture period.

3397 STEWART-TREVES SYNDROME. (Ger.) Zschoch, H. (Pathologisches Inst., DDR-18 Brandenburg 12, Anton-Saefkow-Allee 2, East Germany). *Zentralbl. Chir.* 100(14):868-872; 1975.

Stewart-Treves syndrome was observed in a 59-yr-old woman who had been mastectomized for carcinoma cribrosum of the right breast 11 yr earlier. She developed a therapy-resistant lymphedema of the right arm six months after mastectomy, and lymphangiosarcoma nearly 11 yr after mastectomy. A statistical analysis of 114 known cases showed that chronic lymphedema is the only pathogenetic factor involved in Stewart-Treves syndrome, while neither sex, nor the course and therapy of the original carcinoma, nor the age at the manifestation of the original carcinoma or of the lymphedema play any pathogenetic role. Most patients affected by the Stewart-Treves syndrome are cured breast cancer patients.

3398 LYMPHOSARCOMA OF THE BREAST. (Eng.) Ross, C. F. (St. Peter's Hosp., Chertsey, Surrey, England); Eley*, A. *Br. J. Surg.* 62(8): 651-652; 1975.

A 68-yr-old woman presenting with a lump in the right breast underwent a simple mastectomy for a tumor thought to be a medullary carcinoma but which microscopically proved to be a well-differentiated lymphosarcoma. The lesion was considered primary. However, the patient subsequently developed a subcutaneous lump over the left hip followed by an enlarged lymph node in the left groin. The hip tumor closely resembled the breast tumor, while the lymph node tumor resembled reticulum cell sarcoma. The patient responded to chlorambucil but eventually died of bronchopneumonia after developing gross hepatomegaly. Autopsy revealed an undifferentiated malignant lymphoma in the liver and spleen but no deposits elsewhere. Histologically, the tumor resembled that of the involved lymph node. Although the majority of patients with lymphosarcoma die with generalized disease, it is rare for the latter to involve breast tissue. When the breast is first affected and the lesion cured by mastectomy, the tumor presumably arises as a primary in that organ.

3399 EARLY HISTOLOGICAL FINDINGS OF CARCINOMA OF THE BREAST. (Ger.) Aufdermaur, M. (Pathologisches Institut, Kantonsspital, 6200 Luzern, Switzerland). *Radiol. Clin.* 44(4):300-308; 1975.

The case of a 65-yr-old woman who presented with a bleeding breast but no palpable abnormality is described. A 3 cm biopsy sample, which had appeared on mammography as a circular area of small calcified specks, plus the nipple were removed. Histology indicated carcinoma without infiltration or necrosis. Intraductal carcinoma *in situ* was diagnosed. This case demonstrates the value of mammography for locating the useful biopsy specimen in cases of early cancer of the breast.

3400 AN ATLAS OF SUBGROSS PATHOLOGY OF THE HUMAN BREAST WITH SPECIAL REFERENCE TO POSSIBLE PRECANCEROUS LESIONS. (Eng.) Wellings, S. R. (Sch. Medicine, Univ. California, Davis, Calif. 95616); Jensen, H. M.; Marcum, R. G. *J. Natl. Cancer Inst.* 55(2):231-273; 1975.

Dysplastic, hyperplastic, anaplastic, and cancerous lesions in 196 whole human breasts were identified and enumerated by a subgross sampling technique. Of the 196 specimens, 119 were suitable for complete quantitative morphologic analysis of the focal lesions by type. These included 67 breasts obtained at autopsy, 20 cancerous breasts obtained at mastectomy, and 23 breasts contralateral to those with cancer. Morphologic evidence supported the hypothesis that most lesions traditionally classified as mammary dysplasia or fibrocystic disease; including apocrine cysts, sclerosing adenosis, fibroadenomas, various forms of lobules (sclerotic, dilated, hypersecretory, hyperplastic, atypical, or anaplastic), ductal carcinoma *in situ* (DCIS), and lobular carcinoma *in situ*; arose in terminal ductal-lobular units (TDLU) or in the lobules themselves. Isolated foci of DCIS within the TDLU were seen in 60% of five contralateral breasts with clinical cancer and in 20% of 18 contralateral breasts without cancer. Atypical lobules, composed of fewer and larger ductular units than normal lobules and designated type A (ALA), were more common in cancerous or contralateral breasts than in autopsy specimens; they also tended to persist after the menopause. The ALA lesions had a lobular morphology and were terminal structures on the mammary epithelial tree. They showed various degrees of anaplasia from mild to a severity approaching DCIS. The unfolding of the ALA as it progressed to DCIS gave the false impression that the carcinoma originated in ducts, rather than in the TDLU. Normal-appearing lobules and epithelial hyperplasia or small papillomas, each associated with variable anaplasia, were also pre-

sent in termal ducts serving the ALA. These frequently persisted for decades after the menopause, as did apocrine cysts. In autopsied breasts, the frequency of ALA associated with little or no anaplasia decreased after the fourth decade. ALA associated with severe anaplasia and carcinoma in TDLU were rare at any age. These data suggest that ALA derived from the TDLU is precancerous, or is at least a marker for high-risk cancer tissue.

3401 CLINICOPATHOLOGIC REVIEW OF 88 CASES OF CARCINOMA METASTATIC TO THE PITUITARY GLAND. (Eng.) Teears, R. J. (Univ. Michigan Medical Sch., Ann Arbor, Mich. 48104); Silverman, E. M. *Cancer* 36(1):216-220; 1975.

Clinical and pathologic features of 88 cases of carcinoma metastatic to the pituitary gland were reviewed. Cases of direct extension from a nearby primary neoplasm were excluded, as were leukemias and lymphomas. In all cases, 1-4 sections of pituitary were available for histological examination. In 61 cases (69.3%) metastases were localized either in the posterior lobe alone or in the posterior and anterior lobes together; only 12(13.6%) involved the anterior lobe alone. Diabetes insipidus was present in six patients (6.8%), one of whom had clinical panhypopituitarism due to metastatic tumor and necrosis in the anterior pituitary lobe. Breast and lung were the most frequent primary sites in women and men, respectively. Sixty-four (72.7%) of these glands were grossly normal at necropsy. It is concluded that metatases to the pituitary gland occur more frequently in the posterior lobe than in the anterior lobe, and may be reflected clinically by diabetes insipidus in patients with disseminated carcinoma. The authors speculate that some cases of pituitary metastases are missed at necropsy because of the failure to examine the pituitary grossly or microscopically.

3402 ADENOSINE 3',5'-CYCLIC MONOPHOSPHATE AND ADRENAL TUMOR CELL MORPHOLOGY. (Eng.) Kwan, C. N. (Veterans Administration Hosp., Long Beach, Calif. 90801); Wishnow*, R. M. *In Vitro* 10(5/6):268-273; 1974.

Cultured adrenal tumor cells respond to ACTH, cyclic AMP, cholera enterotoxin, and *Escherichia coli* enterotoxin with increased steroidogenesis and a reversible alteration of monolayer morphology from flattened to spherical shaped cells. Studies with CCL 79 cells derived from a mouse adrenal cortex tumor showed that this morphological response was not due specifically to the interaction of ACTH (10 mU/ml) or cholera enterotoxin (50 ng/ml) with a membrane receptor site, since both cyclic AMP (5 mM) and theophylline (5 mM), which work intracellularly, also stimulated steroidogenesis and rounding of adrenal cells. The morphological alteration appeared to be unrelated to stimulation of steroidogenesis or protein synthesis in that cholera enterotoxin in the presence of aminoglutethimide (10 μg/ml) or cycloheximide (14 μg/ml) still caused rounding and cyclic AMP accumulation without increased steroid production. These results suggest that increased intracellular cyclic AMP concentrations may be related to the observed change of flattened adrenal cells to a spherical shape in monolayer culture.

3403 MIXED MESENCHYMAL DIFFERENTIATION IN MENINGIOMAS. (Eng.) Ball, J. (Royal Infirmary, Sheffield S6 3DA, England); Cook, T. A.; Lynch, P. G.; Timperley*, W. R. *J. Pathol.* 116(3): 253-258; 1975.

Case histories of five patients (two men and three women, aged 16-55 yr) with intracranial meningeal tumors showing mixed mesenchymal differentiation are presented. Three patients survived surgical removal of the tumor and showed no signs of recurrence after at least one year; the other two patients died postoperatively. Three of the intracranial tumors contained cartilage; three contained bone; four contained hyaline fibrous strands or nodules, which were calcified in two instances; three contained angiomatous areas; one contained pericytoma-like areas; four contained pleomorphic and sometimes multinucleate giant cells; and one contained a mucoid matrix including spheroidal cells superficially resembling chordoma. These tumors all appeared to have arisen from the meninges and had the properties attributed to mesenchymal cells. These tumors can be misdiagnosed as metastatic deposits, especially in frozen section.

3404 HUMAN NERVOUS SYSTEM TUMORS: OBSERVATIONS BY HIGH VOLTAGE ELECTRON MICROSCOPY. (Eng.) Lyser, K. M. (Hunter Coll., Box 1030, 695 Park Ave., New York, N.Y. 10021). *Acta Neuropathol. (Berl.)* 32(4):313-324; 1975.

Thick sections (0.5-2μ) of biopsies from human nervous system tumors (Schwannoma, ependymoma, medulloblastoma), fixed in aldehydes followed by osmium, and stained with uranyl acetate and lead, were studied at 2.5 million V. They were then compared to thin sections of the same material observed by ordinary low voltage electron microscopy. High voltage electron microscopy permits direct observation of cell fine structure in three dimensions, including the spatial relations of organelles. Details of contours of nuclear envelopes, shapes of mitochondria, fine aspects of the structure of cell surfaces and processes, such as the flat sheet-like and irregular cylindrical processes of Schwannoma cells, the small projections and ridges on their surfaces, and microvilli and cilia of ependymoma cells, and other features have been observed. These initial observations demonstrate the applicability of high voltage electron microscopy to further study of neural neoplasms.

3405 MALIGNANT MESENCHYMOMA: CASE REPORT WITH ELECTRON MICROSCOPIC STUDY. (Eng.) Klima, M. (Veterans Administration Hosp., 2002 Holcombe Blvd., Houston, Tex. 77031); Smith, M.; Spjut, H. J.; Root, E. N. *Cancer* 36(3):1086-1094; 1975.

A malignant mesenchymoma of the thigh was studied

by light and electron microscopy. A 65-yr-old Caucasian man had experienced thrombophlebitis and chronic venous stasis, and presented with a mass in the posterior part of the left thigh. Otherwise, physical and laboratory examinations were within normal limits. Surgical excision exposed a well-circumscribed mass located within the upper parts of the hamstring muscles; the upper tumor pole was near the ischial tuberosity, while the pseudocapsule was in contact with the sciatic nerve. The tumor was excised, and frozen section examination yielded a diagnosis of sarcoma. Despite postoperative radiotherapy and chemotherapy, multiple bilateral pulmonary metastases, hemorrhagic pleural effusion, and death occurred. Grossly, the neoplasm appeared pseudoencapsulated and generally mucoid. Histologically, there were a sparse stroma, focal necrosis, and many transitional areas from cellular leiomyosarcomatous to bizarre myxomatous. The gelatinous areas were varied, generally displaying a large, irregular cell with a large, dark, bizarre nucleus. Electron microscopy revealed a prevalent cell uncharacteristic of a single cell type and no basic ultrastructural differences between the leiomyosarcomatous and the gelatinous areas. The three most differentiated cell types were large ovoid cells, slender cells with occasional fat droplets, and multinucleated giant cells. However, most cells showed transitional patterns, irregular nuclei, and signs of degeneration. While light microscopy favored a diagnosis of leiomyosarcoma or liposarcoma, electron microscopy revealed most cells similar to osteoblasts and chondroblasts. Prognosis was considered poor, and the name mesenchymoma considered proper.

3406 MULTIPLE KERATOACANTHOMAS: ASSOCIATION WITH DEFICIENT CELL MEDIATED IMMUNITY. (Eng.) Claudy, A. (Hopital Edouard Herriot, Lyon, France); Thivolet*, J. *Br. J. Dermatol.* 93(5): 593-595; 1975.

A case of multiple keratoacanthomas associated with deficient cell mediated immunity in a 44-yr-old male Caucasian is presented. Many attempts to restore the lymphocyte function (transfer factor, levamisole) failed but treatments may have had a preventive effect on the development of new lesions. Very few studies of immune defense mechanisms against keratoacanthoma have been made. Keratoacanthoma should remain isolated and heal spontaneously if the cellular immune responses are efficient. This case shows an alteration of *in vivo* and *in vitro* cellular immune responses without any clinical evidence of infection or of other tumors. It appears that cell mediated immunity may play a major role in the defense against keratoacanthoma. Its deficiency may explain the severity of the evolution of the lesions and their recurrences.

3407 FAMILY STUDIES OF MALIGNANT MELANOMA AND ASSOCIATED CANCER. (Eng.) Lynch, H. T. (Creighton Univ. Sch. Medicine, Omaha, Nebr.); Frichot, B. C.; Lynch, P.; Lynch, J.; Guirgis, H. A. *Surg. Gynecol. Obstet.* 141(4):517-522; 1975.

Five cancer-prone families are presented in whom the occurrence of malignant melanoma (one to three cases/family) was associated with a variety of other histologic types of cancer, including an excess of multiple primary malignant tumors. The genetic mode of transmission of cancer in each family is consistent with a dominant factor that has strongly predisposed these patients to a general cancer diatheses. The tumor spectrum included, in addition to malignant melanoma, cancers of the breast, gastrointestinal tract, lung, and lymphoproliferative system. Recently human sarcoma antigens S_1 and S_2 were noted to occur with malignant melanoma and the same variety of tumors noted in these five families. The development of antigenically related tumors and even multiple primary malignant tumors in families prone to malignant melanoma may be due in part to the fact that relatives of the tumor patients share common antigens and possibly blocking antibodies.

3408 CONGENITAL STALKED FIBROMATOUS POLYP OF THE SUPERIOR POLE OF THE TONSIL CONTAINING HAIRLESS SEBACEOUS GLANDS. (Eng.) Schmid, K. O. (Patholog. Institut d. Univ., Auenbruggerplatz 25, A-8036 Graz, Austria). *Beitr. Pathol.* 155(4):435-442; 1975.

A case report of a congenital, stalked fibromatous polyp of the tonsil is reported that is a previously undescribed variant of this tumor type. The patient was a 29-yr-old male in whom a small, whitish, hard polyp was found at the upper right tonsillar pole. The base of the polyp was connected to the palatal musculature. Histologically it was a stalked fibromatous polyp with many epitheliomatous cords at the base, some branched. There was a pronounced epithelial vacuolization and a distinct lobular arrangement reminiscent of sebaceous glands. At the top region, many mature sebaceous glands were found and the squamous epithelium in this region appeared epidermoid and hyperkeratotic. The transformation into parakeratotic keratinized squamous epithelium was sharply delineated and plug formation was less distinct. Duct-like indentations of the epidermis with small, mature sebaceous gland buds were also seen as well as hair bud like areas. Trichoids, real hairs and sweat glands were absent. The connective tissue was dense and contained much collagen Only a small amount of normal tonsil was seen at the base. This polyp exhibits primarily an immature infantile sebaceous nevus, only the top of which is mature. It is felt that this case thus involves a mixed form, i.e., the circumscribed transition of an infantile and immature *Naevus sebaceus*. It is viewed as a dysontogenetic tumor and because of its immature character it is felt to be congenital.

3409 ACHALASIA AND ESOPHAGEAL CARCINOMA: STUDIES IN EARLY DIAGNOSIS FOR IMPROVED SURGICAL MANAGEMENT. (Eng.) Carter, R. (227 West Badillo St., Covina, Calif. 91723); Brewer, L. A., III. *Am. J. Surg.* 130(2):114-120; 1975.

A study was made of 225 cases (four new patients and 221 from the literature) of cancer of the esophagus associated with long-standing achalasia to determine

the salient features in early diagnosis. The four new cases (two men, two women; 40-71 yr old) had suffered from dysphagia and sometimes regurgitation for periods ranging from 12-20 yr before a change in symptoms led to diagnosis of esophageal cancer. All four patients died shortly after diagnosis. The majority of the 221 patients described in the literature were also hospitalized for evaluation of achalasia without suspicion of superimposed cancer. The distinctive clinical features of carcinoma associated with achalasia are: (a) it occurs at an earlier age (48 compared to 64 yr) than does esophageal carcinoma in general; (b) it usually involves the middle third of the esophagus; (c) the lesion is often bulky and polypoid, and predominantly epidermoid; (d) stasis esophagitis from esophageal obstruction is probably premalignant; (e) it is easily missed on esophagography and esophagoscopy; (f) the tumor is rarely resectable; and (g) prognosis is very poor. In a case of achalasia when obstructive symptoms persist, the diagnosis of cancer can be made only if the enlarged esophagus is thoroughly lavaged and emptied of retained food prior to esophagography and esophagoscopy. Tomograms, echograms, and cinefluoroscopic studies may suggest carcinoma. The presence of a tumor is almost certain when obstruction is found above the cardia and the esophagoscopic returns are bloody. Esophageal washings and endoscopic cytologic study and biopsy are highly diagnostic procedures. Since early diagnosis has been so difficult, the lesion has been resectable in only a few cases. In a previous study of 167 cases of achalasia and carcinoma, only 5 of 38 patients who underwent exploration had definitive resection. Esophagomyotomy is the treatment of choice for a symptomatic patient with achalasia, but the operation must be performed early because once megaesophagus has developed, myotomy becomes ineffective. Earlier diagnosis may allow curative resection, and since esophageal carcinoma with achalasia occurs in younger age groups, these patients should be better risks for resection.

3410 ULTRASTRUCTURAL FEATURES OF HUMAN JUVENILE LARYNGEAL PAPILLOMAS. (Eng.) Lundquist, .-G. (Dept. Otolaryngology, Karolinska Sjukhuset, -104 01 Stockholm, Sweden); Frithiof, L.; Wersall, . *Acta Otolaryngol. (Stockh.)* 80(1-2):137-149; 975.

he ultrastructural organization of 12 juvenile laryngeal papillomas was investigated. Four patients ere over 40 yr old, but had carried the disease ince childhood. The other eight patients were 2 o 10 yr old and had carried the disease from 1 to yr. A discontinuity of the basement membrane as regularly observed and the basal cells often xhibited abundant cytoplasmic processes. In the tratum spinosum there were often glycogen-like inlusions as well as Odland bodies and keratohyalin ranules. In the superficial layers there were nulear remnants as in parakeratosis. Virus-like parcles of a diameter around 330 Å were demonstrated n a disintegrated superficial cell. The scarcity f these particles may be due to the fact that transormation of the unrecognizable viruses, presumably resent in the basal and spinous cells, to the recognizable virus-like particles occurs rarely in these tumors, due to the high shedding rate.

3411 MULTIPLE PRIMARY CARCINOMAS OF RESPIRATORY TRACT: PRIMARY CARCINOMA OF LARYNX FOLLOWED BY PRIMARY CARCINOMAS INVOLVING TWO LUNGS CONSECUTIVELY. (Eng.) Sakula, A. (Redhill General Hosp., Surrey, England). *Br. J. Dis. Chest* 68:128-136; 1974.

A case report is presented of a heavy cigarette smoker who developed multiple primary carcinoma of the respiratory tract. A 53-yr old man developed a primary, well-differentiated, squamous-cell carcinoma of the larynx which was successfully treated by total laryngectomy and block dissection of the involved cervical lymph nodes. He developed a primary oat-cell carcinoma with areas of squamoid appearance in the left lower lobe bronchus 2 1/2 yr later. This condition was successfully treated by lobectomy and radiotherapy. The patient remained well for the next ten years before developing another primary carcinoma of oat-cell type in the right main bronchus and right upper lobe that infiltrated the outer wall of the right pulmonary vein. At autopsy there was no evidence of malignant disease in any other organ. This is the first reported example of a primary carcinoma of the larynx followed by independent development of primary carcinomas first in one lung and then in the other. The time intervals between the three primary carcinomas and their different histological patterns and the autopsy findings did not suggest any connection between them. The family history revealed several cases of primary lung cancer, suggesting that the patient might be prone to cancer. It is suggested, however, that the more likely explanation is the exposure of the larynx and bronchi to a common carcinogenic agent, such as cigarette smoke. This explanation is strengthened by the observation that all reported cases of multiple cancer of the respiratory tract have occurred in 50-70-yr-old men who were heavy cigarette smokers.

3412 ON PLEURAL MESOTHELIOMAS. (Rus.) Bogush, L. K. (Moscow City Hosp. Tuberculosis, No. 7, Moscow, USSR); Zharakhovich, I. A.; Kubrik, N. E.; Rasshivalov, S. K.; Ermolaev, K. K.; Shmelev, M. M.; Lavrent'eva, N. B. *Vopr. Onkol.* 47(6):3-8; 1975.

Pleural mesotheliomas were studied in 19 patients (ten men and nine women). Their ages were 21-60 yr, with five older than 40 yr. In 13 patients, the diagnosis was established by means of the data gained with biopsy and surgical procedures; in the remaining six, the pathological condition was found at autopsy. Based on the clinical-radiological picture, the patients were divided into three groups: (1) four patients without exudative accumulation during the development of the mesothelioma; (2) seven patients with exudative accumulation in the pleural cavity; and (3) eight subjects with the tumor developing at the site of a pneumothorax which had been induced years before. In patients in group 1, the pathological process was revealed by fluorography. The subjects of group 2 had been originally treated

unsuccessfully for tuberculosis or cardiac decompensation; the first symptom of the diease was the occurrence of serous exudate determined by needle biopsy, with a sensation of pressure in the affected area. In group 3, pneumothorax was applied to treat infiltrative and focal tuberculosis. Subsequently, the mesothelioma developed over a period of 13-24 yr; this was based on gradual exacerbation of postpneumothoracic pleural empyema, for which the patients had been treated. Aspiration of the empyema showed the presence of serous-purulent or hemorrhagic exudate. X-rays revealed encapsulation of the empyemic cavity. The prognosis of mesothelioma is poor, with the diffuse variety of the disease ending in death only months after surgery. In some cases, postsurgical life expectancy of the nodular type of the disease reaches 5-9 yr.

3413 HISTOLOGIC TYPES AND POSSIBLE INITIAL STAGES IN EARLY GASTRIC CARCINOMA. (Eng.) Grundmann, E. (Pathologisches Institut der Universitat, D-44 Munster i. W., Westring 17 West Germany). *Beitr. Pathol.* 154(3):256-280; 1975.

A study was undertaken to determine which zones of the human stomach may be liable to carcinomatous degeneration. Among 2003 gastric specimens from 301 patients, a diagnosis of carcinoma was made in 45 cases. Examination of resection preparations revealed 36 cases of deep invasive stomach carcinoma and nine cases of early gastric cancer confined to mucosa and/or submucosa. Carcinomatous proliferations limited to mucosa or submucosa were classified in three histologic types: intestinal (adeno), mucocellular (signet ring cell), and anaplastic (solid) type of early gastric cancer. Mixed types were found, which combined the first and the second, or the second and third types. One case presented a mixture of all three types. Possible precursor or initial stages of all types were found in 31 biopsies. Some of these were glandular lesions in superfical parts of the mucosa. "Signet ring cell drippings" from lower parts of tubule necks were recorded as an initial form of the signet ring cell type. The process is interpreted as a detaching of isolated signet ring cells from a gland neck zone in progressing atypical transformation. An early neoplastic stage of the anaplastic (solid) type of early gastric cancer was identified in the "gland neck dysplasis" located exclusively in the antrum between surface mucosa and antrum glands. This lesion was rich in cells and stretched like a broad ribbon. These results confirm the suggestion that the region of gland necks must be a critical zone of transformation and as such, they must be the decisive point of origin of early gastric cancers.

3414 PREMALIGNANCY OF THE MUCOSAL POLYP IN THE LARGE INTESTINE: II. ESTIMATION OF THE PERIODS REQUIRED FOR MALIGNANT TRANSFORMATION OF MUCOSAL POLYPS. (Eng.) Kozuka, S. (Nagoya Univ. Sch. Medicine, 65 Tsurumaicho, Showaku, Nagoya, 466, Japan); Nogaki, M.; Ozeki, T.; Masumori, S. *Dis. Colon Rectum* 18(6):494-499; 1975.

The relationship between the histologic gradation of mucosal polyps in invasive cancer with the age of the patient was studied. Histological specimens of 331 mucosal polyps from 324 patients and 261 invasive carcinomas were used. The polyps were graded on the basis of epithelial psuedostratification. While the ages of the patients had a very wide distribution, the average age increased gradually with the advance of histologic atypism. The average age was 40.7 yr for patients with grade 0 or I polyps (enlargement of the glandular lumens) 45.6 yr for those with crowded tall and narrow epithelial cells (grade II), 47.3 yr for those displaying apparent pseudostratification of the glandular epithelial cells (grade III), 50.4 yr for case of severe pseudostratification (grade IV), and 55.1 yr for those patients displaying extremely severe pseudostratification of the glandular epithelium (grade V). The average age of patients in the autopsy series was 58.7 yr; the peak autopsy incidences of rectum and colon carcinomas were 60-65 yr for females and 65-70 yr for men. A discussion of provisional estimates suggested that a long period, an average of approximately 15 yr, might be required for transition of the early stage of hyperplasia to invasive cancer. Such a transition might be a function of the weakness and/or intermittence of carcinogenic stimulation. Examination and polypectomy at five year intervals after age 35 was hence suggested as sufficient to protect mos people against invasive cancer of the large intestine.

3415 PRIMARY EPITHELIAL TUMOUR IN THE RIGHT ATRIUM OF THE HEART AND INFERIOR VENA CAVA IN NZR/Gd INBRED RATS; PATHOLOGY OF 18 CASES. (Eng.) Goodall, C. M. (Univ. Otago, Dunedin, New Zealand); Christie, G. S.; Hurley, J. V. *J. Pathol* 116(4):239-251; 1975.

A description is given of the pathological anatomy and structure of tumors found in the heart of a strain of inbred albino rats, NZR/Gd. The tumors occurred in the right atrium or inferior vena cava of approximately 20% of untreated animals, of both sexes, over the age of one year. The tumors were located in the wall of the right atrium in 15 cases and in the inferior vena cava in another three case they appeared to be primary in these sites. The tumors were slowly growing, but eventually malignan Light- and electron-microscopic study showed that the tumors were composed of epithelial alveoli imbedded in a collagenous connective tissue containin spindle cells and thin-walled blood capillaries. The epithelium varied from flat to low columnar, and often secreted mucoid material into the lumina, or sometimes, into surrounding tissue. This tumor, for which the name *atrio-caval epithelial mesotheli-oma* is suggested, very closely resembles a rare epithelial tumor of the right atrium previously described in humans under a variety of names. An underlying embryological anomaly had been postulate in these tumors in humans, and the occurrence of pathologically similar lesions in high incidence in hearts of NZR/Gd inbred rats should help test the hypothesis of genetic and developmental causes in the genesis of this rare cardiac neoplasm.

3416 MULTIPLE MYELOMA IN A PATIENT WITH SICKLE CELL ANEMIA: INTERACTING EFFECTS ON BLOOD VISCOSITY. (Eng.) Anderson, I. S. (George Washington Univ. Medical Center, 2150 Pennsylvania Ave., N.W., Washington, D.C. 20037); Yeung, K.-Y.; Hillman, D.; Lessin*, L. S. *Am. J. Med.* 59(4):568-574; 1975.

The occurrence of multiple myeloma in a patient with sickle cell anemia was studied clinically in relation to the effect on increased blood viscosity. Whole blood viscosity was studied by means of a micro-viscometer, which measures blood viscosity at 37° C over a physiologic shear rate range of 2.3-230 sec^{-1}. Whole blood and plasma were evaluated from the index patient with sickle cell anemia and multiple myeloma (HbSS myelomatosis), a patient with sickle cell anemia (HbSS) and a normal control patient (HbAA). The index patient showed a slight increase in viscosity over the full shear rate and a marked increase at "capillary" shear rates (2.3-11.5 sec^{-1}). The blood was reduced with metabisulfite, and viscosity at rates 750 sec^{-1} was highest in the index patient and higher in HbSS than HbAA. At very low shear rates (under 11.5 sec^{-1}), viscometric measurement of the plasma of the patient was significantly higher than that of the control subject with sickle cell anemia or the normal subject. In RBC from which myeloma protein was removed, the viscometric behavior of the index patient's RBC was not different than the control subjects. It is postulated that the increased frequency of vaso-occlusive crisis that occurred in this patinet was due to interaction of circulating RBC and circulating abnormal immunoglobulin.

3417 ALTERED TISSUE EOSINOPHILS IN HODGKIN'S DISEASE. (Eng.) Parmley, R. T. (Medical Univ. of South Carolina, Charleston, S.C. 29401); Spicer, S. S. *Exp. Mol. Pathol.* 23(1):70-82; 1975.

Eosinophils were studied ultrastructurally and cytochemically in lymph nodes, spleen, lung, and peripheral blood from nine patients with Hodgkin's disease, (7 patients) reticulum cell sarcoma (1) and chronic inflammatory disease (1). When compared with buffy coat eosinophils, the tissue eosinophils showed a marked numerical increase in acid phosphatase and aryl sulfatase-positive small granules, a corresponding decrease in crystalloid granules, and various structural alterations of crystalloid granules. Changes in the tubular vesicular system appeared independent of granule alteration. Eosinophils afforded little or no evidence of exocytosis of cytoplasmic granules of macroendocytic activity and appeared involved in microendocytosis. These studies confirm the previous description of altered crystalloid granules in tissue eosinophils and document the decreased number of crystalloid granules and increased prevalence of small granules in these cells.

3418 SURFACE CHARACTERISTICS OF HODGKIN'S CELLS. (Eng.) Kay, M. M. B. (Natl. Inst. Child Health, Baltimore City Hosp., Baltimore, Md. 21224). *Lancet* 2(7932):459-460; 1975.

In reply to a letter questioning his identification of Reed-Sternberg (RS) cells by scanning electron microscopy, the writer reviews the reasons for apparent differences in the surface of the RS cells described and those tentatively identified as Hodgkin's cells. The differences are ascribable to differences in temperature, pH or culture substrate; methods of fixation and preparation of specimens for scanning electron microscopy; and stages of activation of the cell. The macrophage origin of the RS cells was suggested by the appearance of lamellae and particles on the surface of the cells within 10-20 min after antigen stimulation and by changes in surface ultrastructure during T cell-mediated cytolysis. Further support for a macrophage origin came from the observations of (a) lymphocytes within phagocytic vacuoles of RS cells with phase microscopy, and (b) lymphocytes partially engulfed by RS cells with scanning electron microscopy. This finding might explain the impaired cellular immunity and lymphopenia seen in patients with advanced disease.

3419 ONCORNAVIRUS-LIKE PARTICLES FROM CULTURED BONE MARROW CELLS PRECEDING LEUKEMIA AND MALIGNANT HISTIOCYTOSIS. (Eng.) Vosika, G. J. (Univ. Minnesota Health Sciences Center, Minneapolis, Minn. 55455); Krivit, W.; Gerrard, J. M.; Coccia, P. F.; Nesbit, M. E.; Coalson, J. J.; Kennedy, B. J. *Proc. Natl. Acad. Sci. USA* 72(7):2804-2808; 1975.

Two patients were studied in whom preleukemia was among the diagnostic considerations. Bone marrow from these patients was cultivated for one wk in conditioned media with dexamethasone, then a high-speed pellet of the supernatant fluid and disrupted cells was prepared and analyzed on a sucrose gradient for enzymatic activity characteristic of RNA-related DNA polymerase (reverse transcriptase). Peaks of endogenous DNA polymerase activity showed ribonuclease sensitivity and/or stimulation with the synthetic template poly(rC)-$(dG)_{12-18}$. This was demonstrated in both patients at densities of 1.15 to 1.19 and 1.21 to 1.24 g/ml. Diagnosis two and four months after initial evaluation revealed acute myelogenous leukemia and malignant histiocytosis, respectively. Prior studies had suggested a possible etiological significance of such particles in human leukemia. The demonstration of similar particles preceding clinically overt disease in these patients supports this hypothesis and offers the possibility of early diagnosis and treatment.

3420 ABNORMAL HEMOGLOBIN SYNTHESIS IN SOME LEUKEMIC PATIENTS. (Eng.) Pagnier, J. (Institut de Pathologie Moleculaire, Groupe U 15, de l'Institut National de la Sante et de la Recherche Medicale, Laboratoire associe au Centre National de la Recherche Scientifique, 24, rue du Faubourg Saint-Jacques, 75014 Paris, France); Labie, D. *Biochimie* 57(1):71-76; 1975.

The hemoglobin chain synthesis during leukemic processes was studied in patients (20-50 ml blood from each patient) with fetal hemoglobin ranging from 5-20%. [^{14}C]leucine (40-50 mCi/mM) or [^{3}H]leucine or [^{3}H]lysine (15-40 Ci/mM) served as markers. Regular blood donors with discrete reticulocytosis who had

not been bled in three months served as controls. Radioactive precursor incorporation varied with the reticulocyte count of the sample. After 30-min incubations, the $\beta^A/\alpha A$ specific activity ratios ranged from 1.25-1.55 for the patients compared to 1.08 for controls. The decrease in the ratio observed for the patients after two hours of incubation was caused by a decrease in chain synthesis and stable α synthesis rate. Specific activity ratios for γ^F/α^F showed a balanced synthesis. The α chain specific activity was identical in fetal and adult hemoglobin. In all cases but one, the total radioactivity of non-α chains was greater than that of α chains. The precursors were identified by Sephadex-G100 chromatography; the radioactivity incorporated into the dimeric peak ranged from 2.7-8.7% for the patients, in contrast with 1-2% for the controls. In this peak, the labeling was mainly located in the α chain, and, in four cases, it was all in the α chain. In the controls, radioactivity was found in both α and β chains with a ratio of 0.35. These results suggest a β-thalassemic pattern, in which free α chains are associated with defective chain synthesis. The clonal disorder hypothesis cannot be ruled out.

3421 ULTRASTRUCTURE OF ACUTE MYELOID LEUKEMIA ARISING IN MULTIPLE MYELOMA. (Eng.) Skinnider, L. F. (Dept. Pathol., Univ. Saskatchewan, Saskatoon, Canada); Ghadially, F. N. *Hum. Pathol.* 6(3): 379-384; 1975.

Electron microscopy of bone marrow from a case of multiple myeloma in which acute myeloid leukemia supervened four years after diagnosis showed two distinct populations of neoplastic cells. One population was plasmacytoid, the other myeloid. No intermediate cell types were found. The patient (a 73-yr-old man) was treated first with melphalan 2 mg/day, which was discontinued if the WBC count fell below $4000/mm^3$. Therapy with melphalan discontinued after diagnosis of leukemia. It appears that the acute leukemia in this patient was a distinctly new neoplasm arising from the myeloid series of cells. Since in nearly all previously reported cases, as well as this patient, alkylating agents had been administered, this may have been a factor in the development of acute myeloid leukemia.

3422 CYTOGENIC STUDIES IN MYELOMATOSIS. (Eng.) Jensen, M. K. (Division of Haematology, Department of Medicine B, Aalborg Sygenhus Syd, Aalborg, Denmark); Eriksen, J.; Djernes, B. W. *Scand. J. Haematol.* 14(3):201-209; 1975.

The frequency and types of chromosome abnormalities were studied in bone marrow aspirates from 25 unselected patients with myelomatosis. Their ages ranged from 29-77 yr; 17 were men. Sixteen patients were studied before treatment; the remainder had recieved therapy with either melphalan or cyclophosphamide. Mitoses were classified as plasmocytic only if the mitotic cells corresponded in size and tinctorial characteristics to plasma or myeloma cells. Three types of abnormalities of the chromosome complement were seen: abnormal stem lines, structural aberations, abnormal appearance of the chromatin. Abnormal stem lines were present in seven patients; the remainder had a diploid chromosome complement. In most of the patients including some of those without an abnormal clone, metaphases had a blurred appearance similar to that seen in bone marrow aspirates from patients with acute leukemia. Structural aberrations in chromosomes of some metaphases were seen in many of the preparations obtained before cytostatic therapy. The cytogenetic studies indicate that in the patients with abnormal stem lines in the bone marrow, the chromosome abnormalities are confined to the myeloma cells and are not found in the erythrocytic or granulocytic precursors. Thus, these precursors do not seem to be involved in the neoplastic process. The cytogenic changes in myelomatosis are more uniform than in most other malignant disorders.

3423 CHROMOSOME BANDING ANOMALIES IN ACUTE MYELOID LEUKAEMIA (Eng.) Fleischmann, T. (Natl. Inst. of Oncology, 1525 Budapest, 114, P.B.: 21, Hungary); Bodor, F. *Int. J. Cancer* 15(6):980-984 1975.

The application of chromosome banding in two cases of acute myeloid leukemia are discussed. For a 71-yr-old male without tumor heredity and with symptoms of anemia, 20 metaphases were studied and, in all, the chromosome number was 46. Pseudodiploidy was noted and from the C-group one chromosome was missing; in the D-group, an additional chromosome was observed. For a 62-yr-old female, without tumor heredity and with symptoms of anemia, 20 metaphases were analyzed; in six cells an unusual, sharp, paracentromeric negative band was observed on the long arm of one of the chromosomes 16. Markers were diagnosed on the basis of the minor changes in the banding pattern. It is most likely that normal variability of the banding pattern is wide and for this reason it is difficult to differentiate between polymorphism and rearrangements of the chromosome structure. In these cases, an altered chromosome was observed. The data suggest that minor abnormalities of the banding pattern can occur in acute leukemia.

3424 IS THE CHROMATID GAP A FOLDING DEFECT DUE TO PROTEIN CHANGE? EVIDENCE FROM MERCAPTOETHANOL TREATMENT OF HUMAN LYMPHOCYTE CHROMOSOMES. (Eng.) Brogger, A. (Norsk Hydro's Inst. for Cancer Res., Montebello, Oslo 3, Norway). *Hereditas* 80(1):131-136; 1975.

Human lymphocyte cultures were treated with mercaptoethanol (which is known to denature proteins by breaking S-S bridges, leaving the DNA unaffected) in order to test the hypothesis that chromosome attenuations, constrictions and gaps may be due to conformational changes of the packing proteins. All experiments were performed with lymphocytes from one healthy 40-yr-old man. The plasma layer from heparinized venous blood was collected and prepared for culture with final concentrations of 10^6 nucleated cells/ml and 20% human serum in medium 199. The cultures were stimulated with phytohemagglutinin M and incubated for 72 hr; 2-mercaptoethanol was added in various concentrations at different times before harvest. Meta-

phases were collected for two hours with colcemid. Chromosome preparations were made by air drying after methanol/acetic acid fixation and stained with orcein for analysis of chromosome aberrations. The chromosome damage induced by mercaptoethanol consisted of constrictions and gaps, the majority occurring in one chromatid only. Only a few breaks were observed, and exchanges were not seen at all. The amount of constrictions and gaps increased with dose and duration of treatment. A dose of 10^{-2} M for 24 hr inhibited the mitotic activity, whereas lower doses seemed to stimulate the lymphocytes. The pattern of the induced gaps was non-random, suggesting that the packing proteins must be of different kinds which are distributed differently among the chromosomes. These results indicate that the constrictions and gaps occurred from damage to the protein moiety of the chromosome. The results also support the concept that these aberrations are due to a deficient folding of the chromosome fiber into a metaphase chromatid.

3425 THE ASSOCIATION OF W17 WITH FAMILIAL RENAL CELL CARCINOMA. (Eng.) Braun, E. (Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, Ohio 44106); Strimlan, C. V.; Sigron, A. G.; Straffon, R. A.; Zachary, A. A.; Martee, S. L.; Grecek, D. R. *Tissue Antigens* (2):101-104; 1975.

The possible association of the antigen W17 and renal cell carcinoma (RCC) is presented in a study of three unrelated Caucasian families (A, W, and B). A standard microcytotoxicity technique was used. Each family had two generations with RCC, and there was a high frequency of W17 antigen in the patients (83%) and in unaffected family members (77%). The antigen frequency of W17 in a control group of 485 normal individuals was 10%. Since RCC was examined in families, only one member from each family was considered a random inheritor of W17. Using the control group of 485, the uncorrected P value was 0.0011. When corrected, the P value was 0.066, or of borderline significance. W17 was not found in 13 random cases of RCC. Therefore, W17 may be a "marker" antigen in families. Urography, angiography and years of observation are needed to determine the true incidence of RCC among W17-bearing family members.

3426 LEUKOPLAKIA OF THE URINARY TRACT: A REVIEW. (Eng.) Reece, R. W. (Medical Coll. of Virginia, Virginia Commonwealth Univ., Richmond, Va.); Koontz, W. W., Jr. *J. Urol.* (2):165-171; 1975.

Effects of leukoplakia of the urinary tract are reviewed based on 44 cases. Patients with lower urinary tract involvement present typically with symptoms and findings of recurrent cystitis and only late cystoscopy uncovers the presence of leukoplakia. Typical patients with upper tract involvement present with renal colic and symptoms of recurrent pyelonephritis, and leukoplakia was usually not found until pathology or autopsy specimens were analyzed. Etiologically, numerous theories have been advanced. Leukoplakia may be a metaplastic reaction of normal epithelium to noxious stimuli. Chronic infection probably serves as the major etiologic factor. Avitaminosis A, tuberculosis, syphilis, hormonal changes, and schistosomiasis have also been associated. Grossly, leukoplakia is grayish-white and lesions are described as having a course textural appearance. It may be diffuse or localized and may have sharp or indistinct borders. The plaques are free of vessels yet the underlying mucosa is friable. Microscopically, lesions have a keratinized squamous epithelial appearance. In the current study 18 patients are women and 26 are men and generally a 4:1 ratio is found for lower tract involvement and an equal ratio for upper tract involvement. The right kidney pelvis is more frequently involved. Age of susceptibility ranges from the third to the eighth decade. Radiologically, the pyelogram can be normal or show signs of recurrent infection. Renal washings may show desquamated cells and patients with upper tract involvement may note the passage of tissue upon voiding. Arteriography is nonspecific. Differential diagnosis includes encrusted alkaline cystitis, malacoplakia, or yeast infection. Ten to 20% of cases are associated with carcinoma at the time of diagnosis. In the current series, five squamous cell carcinomas are associated with 36 leukoplakias of the bladder, 2 of 7 in the renal pelvis and 1 of 3 in the urethra. Transitional cell carcinoma, adenocarcinoma and fibrosarcoma may also be found. Treatments are many and varied but no one treatment seems to be effective. Radical surgery is indicated if symptoms are severe and may also remove the malignant potential. Current therapeutic recommendations are to follow the patient as if he had a low grade malignancy.

3427 SERUM LACTATE DEHYDROGENASE ACTIVITY IN PATIENTS WITH TROPHOBLASTIC NEOPLASMS. (Eng.) Sekiya, S. (Chiba Univ. Sch. Med., Japan); Kikuchi, Y.; Kudoh, J.; Takamizawa, H. *Am. J. Obstet. Gynecol.* 121(8):1119-1120; 1975.

The activity of serum lactate dehydrogenase (LDH) in twenty-two patients diagnosed as having histological gestational trophoblastic neoplasms was investigated to determine its possible use as an aid in clinical diagnosis. Samples of venous blood were examined before and after treatment. LDH values were determined by the method of sequential multiple analysis. In all patients, serum transaminase and human chronic gonadotropin (HCG) levels were normal. Total serum LDH activity in patients with choriocarcinoma was higher (488 $\pm$ 83 IU)/l than levels found in hydatidiform mole (241 $\pm$ 25 IU) or in chorioadenoma destruens (161 $\pm$ 7 IU). Serum LDH values in patients with hydatidiform mole or chorioadenoma destruens did not show a good correlation with that of urinary HCG. Facts presented in this investigation suggest the use of LDH values as an aid in the diagnosis of choriocarcinoma and chorioadenoma destruens before treatments are started.

3428 SIGNIFICANCE OF PROLIFERATIVE EPITHELIAL LESIONS OF THE UTERINE TUBE. (Eng.)
Moore, S. W. (Hosp. Univ. Pennsylvania, Philadelphia); Enterline, H. T. *Obstet. Gynecol.* 45(4): 385-390; 1975.

In order to assess the incidence and significance of proliferative epithelial lesions of the oviduct, entire oviducts from 124 hysterectomies were examined. Twenty-three cases (18.5%) exhibited focal tubal epithelial proliferation in at least one of an average of 10.5 examined sections. The lesions showed the following characteristics: (1) an increase in the number of nuclei, which in some cases was the only abnormality, (2) stratification of nuclei in a usually thickened mucosa, and (3) less polarity accompanied by nuclear atypia. Changes seen most often included nuclear enlargement, hyperchromasia, irregularities in shape, indentations in the nuclear membranes, and uneven chromatin distribution. A very few mitoses were seen occurring in sections showing proliferative lesions; two mitoses occurred in a case of severe acute and chronic salpingitis. Papillary formations of various descriptions were found in nine cases. Salpingitis was present in 11 cases; where it was mild to moderate, the epithelial alterations were not qualitatively or quantitatively different from cases in which it was not found. An additional epithelial abnormality consisted of an increase in cytoplasmic volume, with a granular bright acidophilic staining. The frequency of proliferative epithelial lesions when actively sought and the rarity of invasive carcinoma of the oviduct make it unlikely that the lesions represent noninvasive carcinoma. There is no justification for diagnosing and treating these lesions as carcinoma *in situ*.

3429 VAGINAL ADENOSIS: ANALYSIS OF 325 BIOPSY SPECIMENS FROM 100 PATIENTS. (Eng.) Antonioli, D. A. (Beth Israel Hosp., 330 Brookline Ave., Boston, Mass. 02215); Burke, L. *Am. J. Clin. Pathol.* 64(5):625-638; 1975.

The histologic features of vaginal adenosis and its malignant potential were assessed based on a study of 339 vaginal and 30 exocervical biopsy specimens from 100 women aged 12-28 yr. In 77% of the cases, the mothers of these patients had taken diethylstilbestrol (DES) during the pregnancy; 7% of mothers had no such history, and in 16% the history was unknown. For each biopsy specimen showing adenosis, five histologic features were evaluated: gland types; mucosal surface involvement by adenosis; squamous metaplasia of adenosis; inflammation; and epithelial atypia. Eighty-eight percent of the patients were positive for adenosis, and approximately 87% of the patients with positive DES-exposure histories had adenosis. Of the 183 vaginal specimens in which the glands could be evaluated, 66% showed a single type of gland and the rest showed various combinations of two or all three gland types. Mucosal involvement by adenosis as either columnar or metaplastic epithelium was found in 60% of the biopsies, and squamous metaplasia was present in almost 90% of the specimens; the extent of metaplasia varied greatly. Inflammation in association with adenosis was common, acute inflammation and moderate to severe chronic inflammation occurring significantly more frequently in patients with adenosis than in those without adenosis. Although endocervical epithelium was most frequently found in the adenosis-positive specimens, almost 20% of the specimens contained both endocervical and endometrial-tubal cells simultaneously. No glandular dysplasia or carcinoma was identified in these specimens, but in more than half of the specimens the squamous epithelium adjacent to foci of adenosis was abnormal. There was no correlation between any of the gland types and the incidence of combined form of adenosis, the incidence of any extent of squamous metaplasia, or the presence of chronic inflammation. However, there was a correlation between mucosal involvement by adenosis and absent to moderate squamous metaplasia with moderate to severe chronic inflammation. Absence of inflammation was also correlated with the absence of squamous metaplasia.

3430 HUMAN VAGINAL ADENOSIS AND ADENOCARCINOM (Eng.) Sherman, A. I. (No affiliation); Steger, R. W.; Hafez, E. S. E.; Brown, S. *J. Repro Med.* 14(5):221-227; 1975.

The surface ultrastructure of vaginal cells in wome exposed *in utero* to nonsteroidal estrogens was stud ied. Samples of vaginal tissues were obtained from these women, and from unexposed patients undergoing vaginal operations. As a result of the exposure to diethylstilbestrol, some women had cervico-vaginal anatomical abberations; these included pericervical folds or collars, cockscomb projections at the ante rior portion of the cervix, or vaginal constriction. The most striking abnormalities in exposed patients were histological and could be classified into one five groups: (1) complete epidermidization and com plete replacement by metaplasia; (2) surface epider midization, and residual glands beneath the surface (3) incomplete epidermidization, a mixture of colum epithelium on the surface (including crypts and gla like elements), and occasional pockets of columnar cells surrounded by squamous epithelium; (4) surface and subepithelial carcinoma (*in-situ* or invasive); and (5) squamous cell dysplasia. The differences i the five groups can be explained by differences in the extent of metaplasia, the process by which abnormal vaginal glandular epithelium is converted to normal squamous epithelium.

3431 PROPERTIES AND MALIGNANT TRANSFORMATION OF ESTABLISHED RAT LIVER PARENCHYMAL CELLS IN CULTURE. (Eng.) Borenfreund, E. (Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, N.Y. 10021); Higgins, P. J.; Steinglass, M.; Bendich, A. *J. Natl. Cancer Inst.* 55(2):375-384; 1975.

Epithelioid cells from the livers of normal Sprague-Dawley and genetically impaired Gunn rats (a mutant Wistar strain with liver uridine diphosphate glucuronyltransferase deficiency) were established in long-term cultures *in vitro*. The mutant cells grew

s flat, epithelioid cobblestone-type monolayers and howed a diploid karyotype. They secreted rat serum lbumin and proteins into their growth media and ontained aryl hydrocarbon hydroxylase. Six to ight weeks after these cells were transformed by reatment with methylazoxymethanol acetate (2 μg/ml) hey exhibited an irregular, piling growth pattern, cquired the ability to grow in soft agar, and hereafter grew as tumors in mutant hamsters given ortisone and in nude mice. These malignant pindle-cell tumors were reestablished in culture nd still secreted serum albumin. The transformed ells became highly multinucleate when exposed to ytochalasin B and thus behaved like tumor cells. his behavior was not shown by the original cells. ells transformed by benzo[a]pyrene (2-5 μg/ml, 8 hr) failed to grow in soft agar culture or as umor in animals. Cells were not affected by iethylnitrosamine (10-100 μg/ml, 48 hr). This ong-term culture system of liver parenchymal cells ay be of use as a model system in determining ntermediate stages leading to malignancy.

432 KINETICS OF INDUCTION AND GROWTH OF PRECANCEROUS LIVER-CELL FOCI, AND LIVER TUOUR FORMATION BY DIETHYLNITROSAMINE IN THE RAT. Eng.) Scherer, E. (Netherlands Cancer Inst., Amterdam, The Netherlands); Emmelot, P. *Eur. J. ancer* 11(10):689-696; 1975.

ne dose-response relationship of focus (island) nduction by diethylnitrosamine (DENA) in rat liver ells was investigated. Two-thirds hepatectomy was erformed on female Sprague-Dawley rats 20-24 hr rior to the application of DENA by stomach tube. ingle oral doses of 0.3-70 mg DENA/kg resulted in TPase-deficient islands with normal surrounding iver tissue. While no effects were seen at dosages 30 mg DENA/kg, 50 mg/kg significantly retarded liver egeneration. A direct proportionality occurred etween the number of islands induced and the DENA ose when the dosage range was 0.3-30 mg/kg. At 0-140 mg/kg DENA, the curve relating number of slands to dose leveled off; this was interpreted s resulting from the toxic action of the carcinoen. A similar relationship existed between dose nd induction of glucose-6-phosphate-deficient or ycogen-retaining islands. Analogous findings esulted from experiments on island induction in the ivers intact (i.e., nonhepatectomized rats receiving 0.9-14 mg DENA/kg daily for four weeks). In tudying liver tumor formation by a single applicaion of DENA after hepatectomy, 50 and 70 mg/kg roduced hepatocellular tumors. The direct proporionality of island induction and the lower DENA oses (0.3-30 mg/kg) suggests that the conversion f a liver cell into an island-forming cell occurs one-hit process. Such one-hit kinetics apply ATPase-deficient, glucose-6-phosphate-deficient, nd glycogen-retaining islands. It is further sugested that toxic effects of carcinogens below the rotetnal level may be significant in carcinogenes, and that the enhancing effect of cell proliferion is exerted at and beyond the induction stage roper.

3433 INTRACISTERNAL A-PARTICLES IN TRANSPLANTABLE MURINE TERATOMAS. (Eng.) Spence, A. M. (Stanford Univ. Sch. Medicine, Stanford, Calif. 94305); Vandenberg, S. R.; Herman, M. M. *Beitr. Pathol.* 155(4):428-434; 1975.

Intracisternal A-particles observed by electron microscopy in transplantable murine teratomas, are reported. Teratoma OTT 2466 consisted of uniform sheets of large, undifferentiated cells with occasional rosette and tubule formation. Many intracisternal A-particles, 80-100 nm in diameter were seen and were composed of two concentric electrondense shells surrounding a 40 nm electron lucent core. OTT 6050 demonstrated A-particles with the same features as above in a few of the stem cells, in the ecto- and endodermal layers of the embryoid bodies, in the cells of primitive neural and respiratory epithelial cells, and in the cells of primitive neuroepithelial rosettes. In the tissues of A/He and 129 strain female mice not receiving tumor transplants, rare intracisternal A-particles were found only in the thymus of the A/He mouse. In the offspring of the cross between these strains and in 129/Sv strain males, the particles were found in the thymus and spleen only. No intracytoplasmic A-, B-, or C-particles were seen in any of the above, and immunofluorescence failed to demonstrate detectable levels of radiation leukemia virus antigen in suspensions of OTT 2466 of OTT 6050. Immunodiffusion failed to reveal levels of group-specific antigens to the Moloney sarcoma virus-murine lukemia virus complex in either teratoma. The negative viral immunoassays indicate the absence of C-particles in each teratoma and the absence of cross reactivity between A- and C-particles. These findings add the OTT 2466 teratoma and the A/He mouse to the list of experimental mouse strains and tumors that contain intracisternal A-particles; they also confirm the presence of these particles in the 129/Sv mouse strain and in the OTT 6050 teratoma. The intracisternal A-particles are not confined to stem cells or embryoid bodies of OTT 6050 and occur in other cell types.

3434 MORPHOLOGICAL OBSERVATIONS OF DYSPLASTIC GLIOMAS HETEROTRANSPLANTED TO EXPERIMENTAL ANIMALS. (Eng.) Gluszez, A. (Inst. Pathol., Med. Acad. Lodz, Poland); Alwasiak, J.; Papierz, W.; Lach, B. *Acta Neuropathol. (Berl.)* 31(1):21-28; 1975.

Morphological analysis of malignant dysplastic gliomas during consecutive transplantation in guinea pigs was carried out. Of 15 transplanted gliomas, successful tumor growth in the anterior chamber of the eye was obtained in five cases. These tumors were examined histologically and explanted *in vitro*. Each tumor was transplanted in a group of 3-5 animals. When the tumor had grown to fill the entire anterior chamber, it was retransplanted into other groups. In three of the successful transplants, only one passage was obtained. In the other cases, 2 and 4 subsequent passages were obtained. Filling of the whole anterior chamber by the tumor took an

average of ten months. The tumors contained cells with abundant cytoplasm and/or monstrous, atypical cells which outnumbered smaller anaplastic cells. The tumors showed regressive changes (e.g. necrosis) and stromal proliferation. Where four successive passages were obtained, there was an intensive proliferation of the small-cell components and growth time was unusually short; filling of the chamber took only four months. Small cells similarly showed expansive growth while cells rich in cytoplasm showed slow growth and degeneration in tissue culture. The small vital potential of the cytoplasm-abundant cells, regressive changes, and stromal proliferation thus appear to inhibit survival of dysplastic gliomas. Further investigation of dysplastic changes and whether or not they are of form of degeneration which disappears during multiple passages is indicated.

3435 PLASMA MEMBRANE ALTERATION ASSOCIATED WITH MALIGNANT TRANSFORMATION IN CULTURE. (Eng.) Gilula, N. B. (Rockefeller Univ. New York, N.Y. 10021); Eger, R. R.; Rifkin, D. B. *Proc. Natl. Acad. Sci. USA* 72(9):3594-3598; 1975.

The intramembrane organization of the plasma membranes of nonmalignant cells in culture was compared by freeze-fracturing with that of virally-transformed malignant cells. No dramatic differences were in the distribution of intramembrane particles in the plasma membranes of these cells when the cells were examined without fixation or with mild fixation (glutaraldehyde treatment) prior to freezing. However, a redistribution of intramembrane particles into aggregates occurred in the membranes of nontransformed cells after treatment with glycerol. The aggregation of particles was extensive in normal chick embryo fibroblasts, and less extensive in mouse 3T3 cells. The glycerol-induced particle redistribution was not inhibited at 4C, but was inhibited by pretreatment with 2.5% glutaraldehyde. A significant number of the cells remained viable after the glycerol treatment, and the process was reversible. Particle aggregation did not appear to be related to either growth rate or cell density. Transformed Rous sarcoma virus/chick embryo fibroblasts and simian virus 40/3T3 cells had few particle aggregates after glycerol treatment. The plasma membranes of chick embryo fibroblasts transformed with a mutant of Rous sarcoma virus (TS-68) that is temperature sensitive for transformation, had few particle aggregates when grown at the permissive temperature (37 C). Extremely prominent particle aggregates were present in the plasma membranes of cells grown at the nonpermissive temperature (41 C). These observations indicate that there is an alteration in the plasma membrane associated with viral transformation which is related to a glycerol-sensitive mechanism that controls the distribution of intramembrane particles.

3436 CONTRIBUTION TO THE KNOWLEDGE OF MYOSITIS OSSIFICANS LOCALISATA. (Cro.) Silobrcic, F. (General Hosp., 58000 Split, SFR, Yugoslavia); Posinkovic, B. *Libri Oncol.* 3(4):295-300; 1974.

3437 MYXOMA OF THE JAW BONES: REVIEW OF LIT ATURE AND HISTOLOGIC REPORT OF 3 CASES. (Eng.) Mosadomi, A. (Harvard Sch. Dental Medicin Boston, Mass. 02115). *J. Natl. Med. Assoc.* 67(3) 196-199, 255; 1975.

3438 A PERPLEXING MALIGNANT BONE TUMOR: HIG MALIGNANT SO-CALLED ADAMANTINOMA OR NON TYPICAL EWING'S SARCOMA. (Eng.) van Haelst, U. G. M. (Dept. Pathology, St. Radboud Hospital, Uni Nijmegen, The Netherlands); van Dorsser, A. H. d. H. *Virchows Arch.* [*Pathol. Anat.*] 365(1):63-74; 1975.

3439 BREAST DISEASE. A CLINICAL STUDY WITH SPECIAL REFERENCE TO DIAGNOSTIC PROCEDU (Eng.) Johnsen, C. (Dept. Surgery II, Univ. Gote- borg, Sweden). *Acta Chir. Scand.* [*Suppl.*] 454:1-108; 1975.

3440 SQUAMOUS METAPLASIA OF CYSTOSARCOMA PHY LODES: A CASE REPORT. (Jpn.) Tominaga T. (Res. Inst. for Microbial Diseases, Osaka Univ. Osaka, Japan); Tei, N.; Kitamura, M.; Taguchi, T.; Koyama, H.; Wada, A.; Taniguchi, H. *Gan No Rinsho* 21(6):411-414; 1975.

3441 THE ULTRASTRUCTURE OF MIXED MAMMARY GLA TUMOURS IN BITCHES. III. THE EARLY STA OF THE MYOEPITHELIAL PROLIFERATION. (Ger.) Bom- hard, D. (Lehrstuhl fur Allgemeine Pathologie und Pathologische Anatomie am Institut fur Tierpatholo gie der Universitat Munchen, D-8000 Munchen 22, Ve erinarstrasse 13, West Germany); Sandersleben, J. *Virchows Arch.* [*Pathol. Anat.*] 367(3):219-229; 197

3442 CARCINOMA OF MALE BREAST. (Eng.) Wetch ler, B. B. (Mount Sinai Hosp. Services a City Hosp. Center, Elmhurst, N.Y.); Futterman, S.; Glatstein, N.; Papatestas, A.; Perlberg, H. J. *N. State J. Med.* 75(8):1226-1228; 1975.

3443 CARCINOMA OF THE BREAST OCCURRING IN A HUSBAND AND WIFE. (Eng.) Wetchler, B. B (Mt. Sinai Hosp., New York, N.Y.); Simon, B. *Mt. Sinai J. Med. N.Y.* 42(3):205-206; 1975. 206; 1975.

3444 BLOOD VESSEL INVASION IN THE PRIMARY SIT AND INVOLVED LYMPH NODES OF BREAST CANCE ITS SIGNIFICANCE TO HEMATOGENOUS METASTASES. (Eng Izuo, M. (Gunma Univ. Sch. Med., Maebashi, Gunma, Japan); Akabane, K.; Okano, A.; Kawai, T. *Jpn. J. Clin. Oncol.* 5(1):53-58; 1975.

3445 ENZYME HISTOCHEMICAL PATTERNS IN HUMAN TUMOURS--I. HYDROLYTIC ENZYMES IN CARCI NOMA OF THE COLON AND THE BREAST. (Eng.) Koudsta J. (Dept. Pathology, "SSDZ", Stichting Samenwerkin Delftse Ziekenhuizen, Reynier de Graefweg 7, Delft

Holland); Makkink, B.; Overdiep, S. H. *Eur. J. Cancer* 11(2):105-109; 1975.

3446 ENZYME HISTOCHEMICAL PATTERN IN HUMAN TUMOURS--II. OXIDOREDUCTASES IN CARCINOMA OF THE COLON AND THE BREAST. (Eng.) Koudstaal, J. (Dept. Pathology, "SSDZ", Stichting Samenwerking Delfte Ziekenhuizen, Reynier de Graefweg 7, Delft, Holland); Makkink, B.; Overdiep, S. H. *Eur. J. Cancer* 11(2):111-115; 1975.

3447 INVASIVE AND METASTASIZING CARCINOMA IN A SMALL ADENOMATOUS POLYP OF THE COLON: REPORT OF A CASE WITH DEMONSTRATION OF A TUMOR ASSOCIATED ANTIGEN. (Eng.) Strauss, R. A. (Presbyterian Hosp., New York, N.Y.); Pascal, R. R. *Hum. Pathol.* 6(2):256-259; 1975.

3448 ADENOCARCINOMA ARISING IN A DIVERTICULAR ABSCESS OF THE COLON: REPORT OF A CASE. (Eng.) Hines, J. R. (Northwestern Univ. Med. Sch., Chicago, Ill.); Gordon, R. T. *Dis. Colon Rectum* 18(1):49-51; 1975.

3449 PROGNOSTIC EVALUATION OF REGIONAL LYMPH NODE MORPHOLOGY IN COLORECTAL CANCER. (Eng.) Tsakraklides, V. (Memorial Sloan-Kettering Cancer Cent., New York, N.Y.); Wanebo, H. J.; Sternberg, S. S.; Stearns, M.; Good, R. A. *Am. J. Surg.* 129(2):174-180; 1975.

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See also:

* (Rev): 3010, 3020, 3021, 3022, 3023, 3062, 3063, 3064, 3065, 3066, 3067, 3068, 3070
* (Chem): 3078, 3080, 3087, 3106, 3107, 3119
* (Viral): 3222, 3226, 3250
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3503 THE COMPARABILITY OF CANCER INCIDENCE RATES. (Eng.) Linden, G. (No affiliation). *Recent Results Cancer Res.* 50:141-147; 1975.

Problems in assessing the validity and comparability of cancer incidence data were examined. A cancer incidence rate was defined as the rate at which cancer cases arise in a specified population during a given time period. The numerator of the rate shows the number of new cancer cases, and the denominator (usually 100,000), the population at risk. The validity of census data in determining the population at risk was questioned, especially because different definitions of racial, ethnic, religious and other subgroups do exist, and because of the difficulty in estimating a population for intercensal years. Various definitions have been put forth for the meaning of new cancer cases, and these include dates of onset of disease, diagnosis, treatment, hospital or clinic admission, pathologic verification, discharge, death, and recording of the case. Incidence rates should be based on the completeness of recording; this is not only difficult to obtain, but even more difficult to evaluate. The critical factor is distinguishing between prevalence and incidence. Prevalence cases can be included in the calculation of incidence rates by the inclusion of previously diagnosed hospital cases, non-hospital cancer deaths, or because there has been a change in the method and time of diagnosis, in the frequency of the use of a new technique, and the finding of occult malignancy at autopsy. Publication of worldwide cancer registry data, and criteria for these data, and the establishment of guidelines for computation and publication of cancer incidence rates are all necessary steps that must be taken if valid, comparable rates are to be produced for the epidemiologic assessment of cancer in various populations.

3504 COMMON GEOGRAPHY AS A CLUE TO CAUSATION. *(Eng.)* Burkitt, D. P. (Medical Res. Council, London, England); Tunstall, M. *Trop. Geogr. Med.* 27(2):117-124; 1975.

The geographical distribution of certain diseases characteristic of modern western civilization (ischemic heart disease, diverticular disease of the colon, gallbladder disease, hiatus hernia, and cancer of the colon) and their prevalence in different sections of a community were examined in an attempt to find common causative factors. Published information concerning the geographical distribution of these diseases was supplemented with the results of questionnaires sent regularly to over 130 rural hospitals in more than 30 countries. The prevalence of each disease was recorded as "high", "intermediate", or "low", and world wide distribution patterns were sketched. Several factors are apparent from the distribution map: (a) the worldwide distribution of each of these five diseases is approximately similar; (b) the prevalence of each disease is maximum in the affluent west, minimal in developing countries (such as Africa and New Guinea), and intermediate in countries between these extremes (such as the Middle East and India); (c) the prevalence in Caucasian and black Americans is comparable; and (d) there is a total contrast between the prevalence in Caucasian and black South Africans. These diseases all not only have their maximum prevalence in the most economically developed countries, but also their prevalence rises first in the upper socio-economic groups of the developing countries. All available information suggests that the prevalence of these diseases in the Western world has increased markedly during the present century, and that they were significantly less prevalent 40 yr ago in black than in Caucasian Americans. It is suggested that the over-refining of carbohydrate foods, which results in fiber-depleted diets, is an etiological factor that is consistent with available epidemiologic evidence on the diseases.

3505 TRENDS FOR TOTAL CANCER DEATHS IN MISSOURI AND THE UNITED STATES: 1950-1967. (Eng.) Edmonds, L. E. (Environmental Health Surveillance Center, Univ. Missouri, Columbia); Marienfeld, C. J. *Mo. Med.* 72(8):499-501; 1975.

Cancer mortality trends in Missouri and in the U. S. from 1950-1967 were compared. White male death rates for all malignant neoplasms have increased both in Missouri and in the U. S. for nearly every 10-yr age group between the ages of 25-84. The exception is the 25- to 34-yr age group, in which the very low death rates have remained unchanged. In contrast, white female death rates since 1950 have decreased in every age group, both in Missouri and in the U. S. as a whole. The U. S. male death rates have increased by 1-24% in every age group, except those beyond age 34. The Missouri cancer death rates in these groups have increased from 18-33%. By 1967, the Missouri male death rates had become higher than the U. S. rate in every age group except the 65- to 74-yr group; the increase was due predominantly to deaths from respiratory cancer. White female death rates for both the U. S. and Missouri have declined by 6-21% in the various age groups, the smallest decline occurring in the 45- to 64-yr age group. Total cancer death rates are higher for women until about age 55, after which the male rates become higher and remain higher. This pattern change is attributed to the higher female reproductive cancer death rate in women under 55, and to the greatly increased respiratory cancer death rate among the older male population.

3506 TUMOR FREQUENCY IN AUTOPSY CASES. I: FREQUENCY AGE AND SEX DISTRIBUTION, PRIMARY LOCALIZATION. (Ger.) Rudiger, K. D. (Pathologisches Institut der Medizinischen Akademie Erfurt, 50 Erfurt, Nordhauser Strasse 74, East Germany); Guthert, H.; Wockel, W.; Hochheim, A. *Zentrabl. Allg. Pathol.* 119(3):194-207; 1975.

The frequency, age and sex distribution, and localization of primary malignant epithelial and nonepithelial tumors were studied with respect to 22,155 autopsies (12,212 men, 9,943 women) during the period 1950-1966. The overall number of malignant tumors was 7,533 (34.2%), of which 99 cases were eliminated because of the unknown location of the primary tumor. The remaining 7,442 cases (33.6%) were distributed among 3,987 men (32.6%) and 3,455 women (34.7%). The frequency difference was statistically signifi-

cant. Malignant epithelial tumors were found in 5,559 cases (25.3% of autopsies; 75.2% of malignant tumors), including 2,945 cases in men, and 2,654 cases in women. Malignant nonepithelial tumors were found in 1,843 cases (8.3% of autopsies, or 24.8% of all malignant tumors), including 1,042 in men, and 801 in women. The frequency of epithelial tumors in both sexes and in men separately was highest in the age range 65-69 yr, and in the range of 60-64 yr in women. The frequency of nonepithelial tumors was highest between 60 and 64 yr in both sexes together and in men separately, and between 55 and 59 yr in women. In men, the organ-specific frequency decreased in the order: lung, stomach, hemopoietic-lymphatic system, colon and CNS. The corresponding order established for women was: reproductive organs (excluding mammae), stomach, colon, hemopoietic-lymphatic system, and CNS.

3507 PHEOCHROMOCYTOMA IN BLACKS. (Eng.) Chung, E. B. (Howard Univ. Coll. Med., Washington, D.C.); Pressoir, R. *J. Natl. Med. Assoc.* 67(1):22-26; 1975.

During the period 1958 to 1973 (16 yr) only five patients with pheochromocytomas were discovered at the Howard University-Freedmen's Hospital. All of the patients were black (two men and three women). They ranged in age from 31 to 66 yr. The tumor was located in the right adrenal in four cases and in the left retroperitoneum in one. In two cases, the tumor was successfully removed surgically and one of these was diagnosed preoperatively. The remaining three cases were found at autopsy. The incidence of pheochromocytoma was 0.08% of autopsies and 0.003% of routine surgicals which is comparable to that of whites. In all but one patient, the tumor originated in the right adrenal gland, the other was extra-adrenal. A history of hypertension was present in four of five patients. Pheochromocytoma should be considered in the diagnosis of every case of hypertension and appropriate screening tests made since this form of hypertension is surgically curable. A brief review of the literature is presented.

3508 MASS SCREENINGS FOR CERVICAL CANCER IN FINLAND 1963-71; ORGANIZATION, EXTENT, AND EPIDEMIOLOGICAL IMPLICATIONS. (Eng.) Hakama, M. (Finnish Cancer Regist., Helsinki); Joutsenlahti, U.; Virtanen, A.; Rasanen-Virtanen, U. *Am. Clin. Res.* 7(2):101-111; 1975.

A mass screening program to help eradicate cervical cancer was undertaken by the Finnish government with the cooperation of individual municipalities. Up to 100,000 smears are taken annually from more than two million women. About 400,000 smears were taken during the period 1963-71; the detection rates per 10^5 were found to be 69 for invasive cancer, six for microinvasive carcinoma, 168 for carcinoma *in situ*, 127 for dysplasia of high degree. Those previously married, and those experiencing bleeding on sexual intercourse, formed high risk groups (relative risks 2 and 6) whereas those previously electro-coagulated had a relative risk of 0.13 only. Probably no changes will occur in the time trends of mortality rates as a result of the screening. The incidence of invasive carcinomas was found to be decreasing by time, although the increase in carcinoma *in situ* cases exceeded this decline.

3509 CANCER OF THE COLON: SOCIOECONOMIC VARIABLES IN A COMMUNITY. (Eng.) Lynch, H. T. (Creighton Univ. Sch. Med. Omaha, Nebr.); Guirgis, H Lynch, J.; Brodkey, F. D.; Magee, H. *Am. J. Epidemi ol.* 102(2):119-127; 1975.

A study was conducted concerning the multiple factor which influence cancer etiology, and to report the distribution of carcinoma of the colon by census tracts in Omaha-Douglas County, Nebraska (population 345,000). A total of 154 cases of colon cancer were diagnosed in 1964 (44.7/100,000). The frequency dis tribution of these patients in specific census tract of this community was determined. Statistical analy sis of the data showed a greater frequency of colon cancer in patients living in census tracts with higher average income. Colon cancer appears to be nonrandomly distributed with respect to the income and socioeconomic status of its victims. However, the causal network linking income and socioeconomic variables to cancer susceptibility must be pursued further. Diet, exposure to industrial pollution, occupational stress, smoking habits, alcohol consump tion, and cultural variations such as food fads may all play a role in assuming responsibility for the differential distribution of colon cancer.

3510 ORAL CONTRACEPTIVES AND BREAST CANCER: PRO GRESS REPORT OF AN EPIDEMIOLOGICAL STUDY. (Eng.) Vessey, M. P. (Univ. Dept. Soc. Community Med., Oxford, England); Doll, R.; Jones, K. *Lancet* (7913):941-944; 1975.

An epidemiological study attempting to correlate the use of oral contraceptives and breast cancer has bee in progress since 1968. Up to the end of June, 1974 322 women (aged 16-45 yr undergoing treatment for newly diagnosed breast cancer) together with 502 control patients, were interviewed at six London hospitals. The interviewing procedure was modified in 1972 to increase the age range from 16-39 to 16-45 yr, to select one control for each cancer patient rather than two, and to match patients and controls in five-yr age groups. Controls were compatible wit the breast cancer patients in regard to age, parity, marital status, date and hospital of admission. The use of oral contraceptives by breast cancer patients and controls was classified by the following parameters: (a) the time when last used before diagnosi (b) the length of the interval between the time contraceptives were first used and the time the breast lump was first noticed, and (c) the total duration of oral contraceptive use. Between 1972 and 1974, 63.8% of the 232 new breast cancer patients had neve used oral contraceptives and the data for the cancer patients and controls corresponded closely. Only 7. of all cancer patients since 1968 had first taken ar oral contraceptive more than eight yr before a lump was first noticed, and only 14.3% had used them for more than two years. It thus appears that the use c oral contraceptives is unrelated to breast cancer.

However, it will be many years before this question can be resolved with certainty.

3511 A HIGH-RISK GROUP FOR BREAST CANCER. (Eng.) Anderson, D. E. (M.D. Anderson Hosp. Tumor Inst., Houston, Tex.). *Tex Med* 71(3):86-90; 1975.

A high-risk, genetically related group of patients for breast cancer is characterized. Breast cancer was assumed to be a composite of several diseases and families with a positive history for the disease composed the study group. A control group was formed of patients with a family history of nonbreast tumors. There was a 15% frequency of bilateral breast cancer in familial patients whose tumors occurred prior to menopause, compared to a 3% rate in nonfamilial patients. Familial patients had an earlier diagnosis that did nonfamilial patients and this effect was more pronounced if the disease was bilateral. Early age and bilaterality were considered to be genetically based. When classed by age at diagnosis, a higher risk was noted among first degree relatives. The risk was five times higher in patients with bilateral disease, three times higher in premenopausal patients, and nine times higher if both factors were present. Further enhancement was noted when patients were classed according to a familial pattern. Three patterns were identified: (a) second degree pedigrees, (b) sister pedigrees, and (c) mother pedigrees. There was a 30% rate among 20- to 30-yr-old sisters of patients whose mothers (mother pedigree) developed the disease (a 47-fold increase over controls). At age 40-59 this declined to a 6-fold excess. A 3-fold excess was noted in sister pedigrees. Cumulative age frequencies indicated that individuals in the high-risk, mother pedigree group developed breast cancer at a rapid rate at an early age (under 50 yr). This high-risk group was also characterized by a high frequency of adenocarcinomas and duct cell carcinomas, and by resemblance between patients and their sisters at age of diagnosis. In addition, the rate of bilaterality was 14% in patients and 15% in their sisters. These results suggest that the mother pedigrees refer to a hereditary form of breast cancer such that an affected mother tends to transmit the disease to approximately 30% of her daughters and that the disease tends to develop bilaterally and prior to menopause.

3512 A STUDY OF BREAST CANCER IN IRISH WOMEN. (Eng.) Herity, B. A. (Dept. Social and Preventive Medicine, Univ. Coll., Dublin, Ireland); O'Halloran, M. J.; Bourke, G. J.; Wilson-Davis, K. *Br. J. Prev. Soc. Med.* 29(3):178-181; 1975.

Because of the high incidence of late-first pregnancies in Ireland, the characteristics of 100 breast cancer patients at St. Luke's Hospital, Dublin were compared with 200 similar-age controls attending fracture clinics in Dublin. The mean ages at first pregnancy were 28.2 yr for those with breast cancer and 27.4 yr for controls. An excess of nonparous women in the group and cancer was not observed. A higher average age of natural menopause (47.33 yr) was found in cancer patients than in controls (45.97 yr). In the control group, 12.5% had undergone hysterectomy compared to 4% of the cancer patients. Significantly greater numbers of cancer patients gave histories of earlier breast trauma. However, these patients may be unusually likely to recall or exaggerate breast traumas.

3513 ESOPHAGEAL CANCER IN ISRAEL: SELECTED CLINICAL AND EPIDEMIOLOGICAL ASPECTS. *(Eng.)* Shani, M. (Chaim Sheba Medical Center, Tel Hashomer, Israel); Modan*, B. *Am. J. Dig. Dis.* 20(10):951-954; 1975.

Clinical and epidemiological aspects of esophageal cancer, based on a nationwide study in Israel, are reported. Records of patients diagnosed as having carcinoma of the esophagus between 1960 and 1966 were reviewed. Three hundred and forty-six newly diagnosed cases yielded a mean incidence of 2.3/100,000. The middle third of the esophagus was the most common site (46%). Seventy-five percent of the tumors were squamous cell carcinoma, 17% were adenocarcinoma, and 4.5% were anaplastic carcinoma. Mean age was 62.3 yr at diagnosis, and the male/female ratio was 1.6:1. Incidence was highest among the Asian-born group (Iran, Turkey, and Yemen) under the age of 60 yr. The most common symptom was dysphagia (83%). Endoscopic examination coupled with X-ray gave a positive diagnosis in 91.5% of the cases. The disease was localized in 37% of the patients, mediastinal in 40%, and there was generalized spread in 23%. Combined surgery and postoperative therapy yielded the best results, but only in a select group of patients. A high operative mortality of 42% was observed, with overall 5-yr survival at 5.8%. The fact that esophageal cancer incidence in persons under 60 yr is highest in Asian-born patients is emphasized. The lack of excess in the older patients in this ethnic group probably represents a lower rate of detection and referral than a recent introduction of a special carcinogen.

3514 THE EPIDEMIOLOGY OF ESOPHAGEAL CANCER IN NORTH CHINA AND PRELIMINARY RESULTS IN THE INVESTIGATION OF ITS ETIOLOGICAL FACTORS. (Eng.) The Co-ordinating Group for Res. on the Etiology of Esophageal Cancer of North China. *Sci. Sinica* 18(1): 131-148; 1975.

An epidemiological survey of esophageal carcinoma covering an area of 14 counties and cities was undertaken in North China. The subjects swallowed a balloon covered with netting to collect exfoliated cells for esophageal mucosa cytosmears. Statistical work on mortality rates was based on (1) roentgen examination, (2) cytological smear, (3) medical history, and (4) inquiry from relatives of deceased. In Linhsien County, a high prevalence of malignant tumors in gullets of poultry were found. Deaths due to cancer of the esophagus accounted for 20% of total deaths in Linhsien County. Analyses of nitrosamines, diethylnitrosamine, dimethylnitrosamine, methylphenylnitrosamine, secondary amines, nitrites and nitrates in food items from Linhsien County were made. *Geotrichum candidum* Link, a fungus found in local pickled vegetables, was studied to determine any relationship to the occurrence of esophageal cancer. The fungus provoked epithelial hyperplasia and papillary growths

in the forestomachs of mice and rats. Experiments with Vitamin C and A were also carried out to determine any relationship between them and esophageal cancer. Vitamin C and A caused a blocking effect when given to rats intubated with methylbenzylnitrosamine or methylbenzylamine and sodium nitrite. Viruses and genetics were not discarded as factors in development of esophageal cancer by the authors. Experiments on animals and clinical trials are still being carried out to find effective methods of neutralizing or inhibiting the carcinogenic properties discussed in association with esophageal cancer.

3515 AN ADDITIONAL YOUNGER-AGE PEAK FOR CANCER OF THE NASOPHARYNX. (Eng.) Balakrishnan, V. (Cancer Res. Inst., Tata Mem. Cent., Bombay, India). *Int. J. Cancer* 15(4):651-657; 1975.

An additional younger-age peak for cancer of the nasopharynx in India is described. Analysis of the case records of 666 patients with nasopharyngeal carcinoma was performed. Of the patients, 535 were male and 131 were female. Age distributions of each sex showed a younger-age peak for males in the 13-22 yr age group. Age distributions according to religious and linguistic groups showed a younger-age peak for Maharashtrian Hindus in the 18-22 yr range; for Gujarati Hindus in the 13-17 yr range; for other Hindus in the 13-22 yr range; and for non-Hindus in the 13-17 yr range. When the group was divided according to the year of diagnosis, the peak for those diagnosed from 1941-1965, and for those diagnosed from 1965-1972, was 13-22 yr for both groups. This study confirms earlier reports of the existance of a younger-age peak for this disease. Because of the occurrence of this peak at the time of transition from adolescence to adulthood, it is suggested that the endocrine changes of maturation may affect the incidence of this type of cancer.

3516 LUNG CANCER AND AIR POLLUTION IN SOUTHCENTRAL LOS ANGELES COUNTY. (Eng.) Henderson, B. E. (Univ. Southern California, Sch. Medicine, 2025 Zonal Ave., Los Angeles, Calif. 90033); Gordon, R. J.; Menck, H.; Soohoo, J.; Martin, S. P.; Pike, M. C. *Am. J. Epidemiol.* 101(6):477-488; 1975.

The possibility that an excess in lung cancer was due to local air pollution prompted an analysis of mortality figures from 1970. An increased rate of lung cancer has been consistently observed from 1968-1972 among males in southcentral Los Angeles. This excess risk occurred across several social classes and occupational categories. No differential excess of oral cavity, pancreatic, laryngeal and bladder cancer was observed in the same area, lessening the possibility that regional variations in smoking habits accounted for the excess lung cancer. For the entire county, occupation was an important determinant of lung cancer risk, but within the limits of proportional incidence statistics, it did not explain the excess male risk in the southcentral area. Air sampling indicated an excess of certain polynuclear aromatic hydrocarbons (PAH) in southcentral Los Angeles. There was a correlation between the geographic distribution of lung cancer cases and the general location of industries which have emitted these PAH. A case-controlled study of smoking, occupational and residential history in the southcentral area is underwa

3517 RELATION BETWEEN LUNG CANCER, CHRONIC BRO CHITIS, AND AIRWAYS OBSTRUCTION. (Eng.) Chaplin, M. (London Chest Hosp., London E2 9JX, Eng land); Festenstein, F. *Br. Med. J.* 3(5985):678-680 1975.

Patients were studied at the London Chest Hospital to discover whether severe airways obstruction, which is associated with chronic bronchitis, is also associated with lung cancer. Two hundred men and 43 women who presented with lung cancer provided information on the prevalence of defined chronic bronchitis and airways obstruction in those suffering from lung cancer. The third group consisted of 223 men presenting with defined chronic bronchitis who were kept under observation to discover how many would die from lung cancer. The results suggested that simple bronchitis and lung cancer often occur together but that obstructive bronchitis and lung cancer do not often occur together. The lack of association between lung cancer and severe airways obstruction requires an explanation.

3518 MORTALITY EXPERIENCE OF A COHORT OF VINY CHLORIDE-POLYVINYL CHLORIDE WORKERS. (Eng.) Nicholson, W. J. (Mt. Sinai Sch. Med., City Univ. New York, N.Y.); Hammond, E. C.; Seidman, H.; Selikoff, I. J. *Ann. N.Y. Acad. Sci.* 246:225-230; 1975.

The medical histories and current health status wer obtained from 255 of 257 Goodyear Tire and Rubber Company employees who had been exposed to polyvinyl chloride (PVC) and vinyl chloride (VC) for a minimu of five yr subsequent to 1946. Observation began ten yr after the onset of exposure. The individual worked in PVC production (majority), maintenance, shipping, and in the laboratory. These workers may often have been exposed to peak VC concentrations exceeding 1,000 ppm. Over 50% of the employees were under age 37 as they entered the cohort. Twenty-four individuals were deceased and three of these deaths were due to liver hemangiosarcoma. On glioblastoma, two lymphomas, and one liver cirrhosi with associated bleeding esophageal varices accounted for other deaths. All of these conditions appear to be associated with VC. The three hemangiosarcomas occurred in individuals exposed prior to 1951. Longer periods of observation are thus needed to study the full spectrum of VC-induced malignancies and their incidence among exposed workers.

3519 THE ASSOCIATION OF VINYL CHLORIDE EXPOSURES WITH MORBIDITY SYMPTOMS. (Eng.) Spirtas, R. (Occupational Health Studies Group, Univ. North Carolina, Chapel Hill, N.C.); McMichael, A. J.; Gamble, J.; Van Ert, M. *Am. Ind. Hyg. Assoc. J.* 36(10):779-789; 1975.

A population of vinyl chloride (VC) polymerization and rubber workers was questioned about job-related illness. Of the workers responding to a mail ques-

tionnaire, 200 were current VC workers and 89 were current workers in the rubber industry. The individual jobs were grouped according to VC exposure (i.e. high, low, and essentially no exposure to VC). As the symptoms under consideration were all transitory and reversible, an acute effects model was employed. Thus, the job was treated as the unit of observation. For the 255 high-exposure group jobs, 37% reported symptoms of dizziness or light-headedness at least once; 12% of the low-exposure group experienced such symptoms. Ten percent of the rubber workers reported these symptoms. Using a series of statistical analyses, the differential exposures to VC among the three study groups accounted for only one of the many possible hazards. A clear dose-response relationship indicated with the symptoms of dizziness, nausea, headache, "pins and needles", and general fatigue. There were also some indications of a dose-response to fainting and eye, nose, or throat irritation. It thus appears that a dose-response relationship exists between certain acute predominantly neurological symptoms and vinyl chloride exposure.

3520 THE USE OF CANCER REGISTRY DATA IN THE INVESTIGATION OF INDUSTRIAL CARCINOGENIC HAZARDS. (Eng.) Waterhouse, J. A. (No affiliation). *Recent Results Cancer Res.* 50:148-154; 1975.

Examples of the use of cancer registry data in the investigation of industrial carcinogenic hazards were examined to illustrate three variations on the fundamental theme of comparison of the observed with the expected number of cases. In the first study, the incidence of scrotal cancer was studied in the Birmingham area and compared to data from the southern areas of London as well as much of the south and east of England. Only the numbers of cases classified by site and year were required to first show the existence of a trend. The national numbers of deaths from this cancer were seen to be approximately equal to the regional number of cases diagnosed. The second basis of comparison was by means of relative incidence (a 2.1:1 frequency in Birmingham over southern England). In a study of the unusually meticulous personnel records of a small factory making a type of alkaline battery, and by making use of the annual incidence rates of the registry classified by site and age, it was possible to compute the number of cancer cases which would be expected to occur in such a group of men followed from their age of entry into the factory until either death or the closing date of the survey. These workers were exposed to cadmium oxide dust, and while there was no difference between expected and observed lung cancer cases, there was a significant difference in the expected (0.58) and observed four cases of prostatic cancer. In a third study on the potential danger of oil mist from machine lubricants a group of factory workers with scrotal cancer were considered as propositi and examined for the development of primary tumors elsewhere. The morbidity rates classified by site and age were used to calculate the expected number: the ages and follow-up for each man from the time of diagnosis. These three studies required, respectively, a high efficiency of registrations for unbiased registrations; registrations in relation to a known population to allow the calculation of reliable morbidity rates by site, sex and age; and a long period of collection and a good follow-up system. These features should be characteristic of a good cancer registry.

3521 EPIDEMIOLOGY OF CANCER IN THE INDIAN SUB CONTINENT. (Eng.) Jussawalla, D. J. (Tata Memorial Centre, Bombay, India); Gangadharan, P. *Indian J. Cancer* 12(1/Suppl.):1-7; 1975.

3522 THE GEOGRAPHICAL DISTRIBUTION OF LEUKEMIA. (Ger.) Mairose, U. B. (I. Medizinische Abteilung des Allgemeinen Krankenhauses Hamburg-Barmbek und I. Medizinische Universitätsklinik Hamburg-Eppendorf, West Germany); Dörken, H. *Med. Klin.* 70(2):53-58; 1975.

3523 DIFFERENCES IN DISTRIBUTION OF LEUKEMIAS IN THE CRACOW REGION IN THE YEARS 1961-1968. (Pol.) Aleksandrowicz, J. (Kliniki Hematologicznej AM w Krakowie, Poland); Janicki, K.; Sliwczynska, B. *Folia Med. Cracov.* 17(1):3-10; 1975.

3524 BURKITT-LIKE LYMPHOMA IN CHILDREN [abstract]. (Eng.) Kaschula, R. O. C. (Children's Tumour Clinic, Groote Schuur, Cape Town, South Africa); Bennett, M. B.; Karabus, C. D. *S Afr Med J* 49(26):1062-1063; 1975.

3525 PRIMARY CANCER OF THE LUNG--A COUNTRY-REPRESENTATIVE SERIES. (Swe.) Kallqvist, I. (Eskilstuna centrallasarett, Eskilstuna, Sweden). *Lakartidningen* 72(44):4291-4295; 1975.

3526 TUMOR FREQUENCY IN AUTOPSY CASES. II. THE MALIGNANT TUMORS OF THE STOMACH. (Ger.) Rudiger, K. -D. (Pathologisches Insitut, Medizinschen Akademie, Erfurt, East Germany); Guthert, H.; Wockel, W.; Saalfeld, J. *Zentralbl. Allg. Pathol.* 119(4):303-315; 1975.

3527 COMPARATIVE CLINICAL-PATHOLOGICAL STUDIES ON PLASMOCYTOMA. (Ger.) Dominok, G. W. (Patholog. Institut Med. Akademie, 8019 Dresden, Fetscherstrasse 74, East Germany); Henker, J.; Heidel, G.; Herold, H. -J. *J. Gesamte Inn. Med.* 30(15):498-502; 1975.

3528 COHORT STUDIES: IN POPULATIONS COVERED BY A COMPREHENSIVE MEDICAL CARE SYSTEM. (Eng.) Shapiro, S. (Johns Hopkins Univ., Baltimore, Md.). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 1-10.

3529 EPIDEMIOLOGICAL STUDIES INTO THE INCIDENCE AND LATENT PERIOD OF ASBESTOS-INDUCED HYALINOSIS, FIBRINOSIS, AND MESOTHELIOMA. (Ger.) Bittersohl, G. (Betriebspoliklinik Leuna, 422 Leuna, Breitscheidstrasse, East Germany). *Z. Gesamte Hyg.* 21(5):369-371; 1975.

3530 SURVEILLANCE OF WORKERS WITH HISTORY OF EXPOSURE TO VINYL CHLORIDE. (Eng.) Perkel, G. (Vinyl Chloride Committee, Industrial Union Dept., AFL-CIO, Washington, D.C.); Mazzocchi, A.; Beliczky, L. *Ann. NY Acad. Sci.* 246:311-312; 1975.

3531 RECORD LINKAGE SYSTEM (WITH SPECIAL REFERENCE TO EPIDEMIOLOGY OF CANCER). (Eng.) Adelstein, A. M. (Office Population Censuses and Surveys, Medical Div., London, England). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 40-43.

3532 LINKAGE OF CENSUS AND DEATH RECORDS TO OBTAIN MORTALITY REGISTERS FOR EPIDEMIOLOGICAL STUDIES IN SWEDEN. (Eng.) Bolander, A.-M. (Natl. Central Bureau Statistics, Stockholm, Sweden). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 36-39.

3533 INFERENCES FROM DATA: DEVELOPMENT OF MATHEMATICAL MODELS. (Eng.) Wagner, G. (German Cancer Res. Center, Heidelberg, West Germany); Tautu, P. *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors)* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 11-17.

3534 ANALYSIS OF TUMOR GROWTH IN RECURRENT MALIGNANT GLIOMAS. (Jpn.) Matsutani, M. (Fac. Med., Univ. Tokyo, Japan); Hoshino, T. *No To Shinkei* 27(3):277-282; 1975.

3535 RATES OF CELL PROLIFERATION *IN VIVO*—PARTITION OF ^{3}H AND ^{131}I INCORPORATED *VIA* IODODEOXYURIDINE [abstract]. (Eng.) Hughes, W. L. (Tufts Med. Sch., Boston, Mass.); Godwin, E. *Proc. Am. Assoc. Cancer Res.* 16:189; 1975.

See also:

* (Rev): 3007, 3008, 3014, 3015, 3024, 3025, 3026, 3038, 3044, 3045, 3046, 3047, 3071, 3072
* (Chem): 3116, 3137, 3148
* (Viral): 3208, 3272
* (Immun): 3307
* (Path): 3439, 3458

3536 CYTOLOGY OF EXPERIMENTAL TERATOMAS AND TERATOCARCINOMAS. (Eng.) Dominis, M. (Sch. Med., Univ. Zagreb, Yugoslavia); Damjanov, I.; Solter, D. *Experientia* 31(1):107-108; 1975.

To determine whether benign could be distinguished from malignant tumors in cytological smears from aspirates obtained with a thin needle, teratomas and teratocarcinomas were produced in C3H/H mice. Transplantation of 7-day-old mouse egg cylinders under the renal capsule of adult isogenic hosts was carried out. After two months, thin needle aspirates were taken from solid tumor areas in ten (sacrificed) tumor-bearing mice. Studies were also made of transplantable neurogenic teratocarcinomas obtained after sequential transplantation of an embryo-derived teratoma. There were five benign embryo-derived tumors and five malignant tumors, differentiated by the presence or absence of undifferentiated stem cells. It was not possible to cytologically distinguish between malignant and benign tumors. All aspirates contained a range of cells from fully differentiated to undifferentiated. Some specific cell types could be identified, but most represented undifferentiated embryonic cells with round or polyhedral nuclei, finely dispersed chromatin, an occasional nucleolus, and a narrow cytoplasmic rim. Only neural cells were identified in aspirates of the neurogenic teratocarcinoma. Also present were smaller, unidentified cells and groups of small cells with a coarse and dense chromatin pattern. Prominent, often multiple nucleoli were seen with both May-Grünwald-Giemsa and hematoxylin and eosin stains. The data are in agreement with previous findings that cells in embryo-derived teratocarcinomas do not basically differ from the original embryonic cells.

3537 MONOLAYER CULTURES OF HUMAN PROSTATIC CELLS. (Eng.) Kaighn, M. E. (W. Alton Jones Cell Science Center, Lake Placid, N.Y. 12946); Babcock, M. S. *Cancer Chemother. Rep. (Part 1)* 59(1):59-63; 1975.

A preliminary account of the isolation, characterization, and preservation of normal prostatic epithelial and carcinoma cell lines is presented. To date, four specimens have been acquired from patients with benign prostatic hypertrophy. Culture attempts have been successful, yielding a total of 2 cell lines. Three of these lines have been examined, and were found to have clearly demonstrable tartrate-inhibitable acid phosphatase granules by histochemical techniques. Problems associated with these studies include the difficulty of (a) characterization of the cells as originating from prostatic epithelium, (b) identification of prostatic carcinoma cells, and (c) possible senescence in culture of cell lines.

3538 *IN VITRO* DETERMINATION OF TRITIATED THYMIDINE LABELING INDEX (LI). EVALUATION OF A METHOD UTILIZING HYPERBARIC OXYGEN AND OBSERVATIONS ON THE LI OF HUMAN MAMMARY CARCINOMA. (Eng.) Meyer, J. S. (Jewish Hosp. St. Louis, 216 N. Kingshighway, St. Louis, Mo. 63110); Bauer, J. C. *Cancer* 36(4):1374-1380; 1975.

A simple method for incubation of tissue specimens (1 mm^3 or smaller) with thymidine methyl-^{3}H (^{3}HTdR) under 3 atm oxygen tension is described. In two spindle cell carcinomas of mouse salivary gland derivation, a plasmacytoma in BALB/c mice, and a mammary carcinoma in C3H mice, this *in vitro* method gave a *in vitro* labeling index (LI) that corresponded closely with the LI determined by injection of ^{3}HTdR *in vivo*. The LI of murine tumors was not affected by storage at 22 C for up to 135 min. The LI of the human carcinomas was constant for at least 75 min at 22 C. The mean LI for 39 invasive human mammary carcinomas was 3.8, but the distribution was skewed to the right, and the most frequently observed LI was between 2 and 3. Larger carcinomas had significantly larger LI than smaller tumors, which suggests that the larger tumors were faster-growing at the time of observation than the smaller tumors. The data suggest that a high LI is associated with more frequent metastasis to axillary lymph nodes.

3539 THE PANCREATIC EPITHELIAL CELL *IN VITRO*: A POSSIBLE MODEL SYSTEM FOR STUDIES IN CARCINOGENESIS. (Eng.) Hay, R. J. (Dept. of Biol. Sci., Wright State Univ., Dayton, Ohio 45431). *Cancer Res.* 35(8):2289-2291; 1975.

A technique is described for the isolation and maintenance in culture of pancreatic epithelial cells from human embryos or neonatal guinea pigs. Minced tissue was dissociated by agitation (120 rpm) for 15 min at 37 C in 0.125% crude trypsin and 0.5% collagenase. Centrifugal fractionation showed that the preparations from guinea pig pancreas were up to 95% acinar cells. Dissociated cells from human material were uncharacterized. Suspensions of dissociated cells were incubated with gyration for 16 to 18 hr, and cell aggregates that formed were placed in stationary culture. Two-dimensional colonial aggregates developed on the plastic substratum. Cells comprising such colonies formed junctional complexes and could be maintained for 20 to 40 days *in vitro*. This system may provide a useful model for studies on pancreatic exocrine cell physiology and carcinogenesis.

3540 HIGH TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE ACTIVITY IN A NEW T-CELL LINE (RPMI 8402) OF ACUTE LYMPHOBLASTIC LEUKEMIA ORIGIN. (Eng.) Srivastava, B. I. S. (Dep. Exp. Ther., Roswell Park Mem. Inst., Buffalo, N.Y.); Minowada, J.; Moore, G. E. *J. Natl. Cancer Inst.* 55(1):11-14; 1975.

The high activity of terminal transferase in a new T-cell-dependent lymphocyte line (RPMI 8402) of acute lymphoblastic leukemic origin is reported. This enzyme resembled the terminal transferase from other human cells in all its properties including K_m (0.7×10^{-6} M for dGTP). The high activity of this enzume in RPMI 8402 and fresh acute leukemia lymphoblasts, in contrast to the low activity of this enzyme reported for "thymus-independent" cells, suggests that this cell line may have originated from leukemia cells. Moreover, the high activity of terminal transferase in RPMI 8402 cells should make feasible large-scale purification of this enzyme for detailed studies.

3541 . DIFFERENTIATION OF ERYTHROLEUKEMIC CELLS *IN VITRO:* IRREVERSIBLE INDUCTION BY DIMETHYL SULFOXIDE (DMSO). (Eng.) Preisler, H. D. (Dept. of Medicine A, Roswell Park Memorial Institute, Buffalo, N. Y. 14203); Giladi, M. *J. Cell. Physiol.* 85(3):537-546, 1975.

This study was made to determine the shortest exposure time to dimethyl sulfoxide (DMSO) needed for the induction of differentiation of Friend erythroleukemia cells and to discover what happens to the differentiating cells when DMSO is removed from the medium. Exposure to DMSO for less than 24 hours failed to produce any detectable evidence of erythroid differentiation. On the other hand, culture in the presence of DMSO for 24 hours followed by culture in DMSO-free medium for four additional days produced a small but detectable increment in the proportion of benzidine positive cells in the culture. Once the differentiation of an individual cell was initiated, the process continued after removal of DMSO from the medium. The cell became progressively more differentiated as evidenced by increases in the intensity of benzidine staining as well as in the rate of heme synthesis and heme content. However, when cells which had been induced to differentiate by DMSO were cultured in DMSO-free medium for more than 3-4 days, they became vacuolated and apparently died. This latter phenomenon, as well as the more rapid proliferation of the undifferentiated cells in the culture, accounts for the observation that when new cultures are established from cultures which have been grown in the presence of DMSO for several days, the culture which results ultimately contains only differentiated cells.

3542 REGULATION OF GROWTH OF MOUSE MASTOCYTOMA CELLS. (Eng.) Davis, J. (Dept. Cell Biol., Univ. Auckland, New Zealand); Ralph, R. K. *Cancer Res.* 35(6):1495-1504; 1975.

The effects of dibutyryl cyclic AMP and theophylline on the growth of the mouse mastocytoma cell line PY815 both *in vivo* and *in vitro*, were investigated. The effect of 4'-(9-acridinylamino)methanesulfon-*m*-anisidine (m-AMSA) on the cyclic AMP and ATP content in this cell line was also studied. PY815 mastocytoma cells were passaged in four DBA x C3H F_1 hybrid mice by serial ip injection of 10^6 cells. Two days later, two mice were given [5-*methyl*-^{3}H]thymidine (26 Ci/mM ip) and the other two mice were given [2-^{14}C]thymidine (62 mCi/mM). After one hour, the latter mice were injected with 7.5 x 10^{-2} M theophylline and 7.5 x 10^{-3} M dibutyryl cyclic AMP (0.2 ml of each substance). Aliquots were subjected to velocity gradient fractionation, and radioactivity was determined. Dibutyryl cyclic AMP (10^{-4} M) and theophylline (10^{-3}M) were added to cultured cells. N^6, O^2-Dibutyryl cyclic AMP plus theophylline inhibited the growth of the mast cell tumor line both *in vivo* and *in vitro*. The inhibitory effect on growth *in vitro* was rapidly reversed following removal of the drugs. Growth inhibition was accompanied by reduced cell surface activity and increased cell-cell adhesion. The drug-treated cells accumulated distinct membrane-bound granules, which are characteristic of more mature mast cells. Treated cells also developed increased amounts of surface-associated acidic mucopolysaccharides. These results suggest that increased intracellular cyclic adenosine 3':5'-monophosphate causes mouse mastocytoma cells to decrease growth and elicits the expression of a more differentiated mast cell phenotype. When log phase cells were treated with 0.04 µg of anti-leukemic m-AMSA, growth ceased and the intracellular cyclic AMP increased from 6-7 pM/10^7 cells to 12-14 pM/10^7 cells in nine hours. When 0.08 µg/ml was used, the increase was from 6-7 to 17-18 pM/10^7 cells. ATP concentration increased from 285 pM/10^5 cells to 1,276 pM/10^5 cells at the same dose over six hours.

3543 KINETIC EVIDENCE FOR CALCIUM-ION AND PHOSPHATE-ION TRANSPORT SYSTEMS IN MITOCHONDRIA FROM EHRLICH ASCITES TUMOUR CELLS. (Eng.) Thorne, R. F. W. (Australian Natl. Univ., Faculty of Science, Canberra, A.C.T., Australia); Bygrave, F. L. *FEBS Lett.* 56(2):185-188; 1975.

The kinetics of Ca^{2+} and phosphate transport by mitochondria from Ehrlich ascites tumor cells were studied. Initial rates of CA^{2+} transport were measured using an ethanedioxy-bis-(ethylamine)-tetraacetic acid-Ruthenium red procedure. In experiments measuring the dependence of initial velocity on the concentration of free CA^{2+}, the latter values were established using Ca^{2+}/nitrilotriacetic acid buffers All of the features of the Ca^{2+} transport system examined were identical to those seen in most mammalian mitochondria. These included the high affinity for Ca^{2+}, the nonlinear relation between initial rates of Ca^{2+} transport and Ca^{2+} concentrate, saturability, high sensitivity to Ruthenium red and La^{3+}, and stimulation by phosphate and acetate. The K_m was 5 µM for free Ca^{2+}, 60 µM for phosphate, and approximately 6 mM for acetate. Ruthenium red inhibited Ca^{2+} transport at concentrations of 80-100 pM/mg protein, while La^{3+} was inhibitory at 15 pM/mg protein. Inorganic phosphate was present in tumor mitochondria (i.e., at zero time) at a concentration similar to that in rat liver mitochondria, and the anion was rapidly accumulated by the tumor mitochondria in a process that was inhibited by *p*-chloromercuribenzoate. The tumor mitochondria had a higher affinity for phosphate than did rat liver mitochondria, both for stimulating Ca^{2+} transport and for it own transport. Because the properties of the Ca^{2+} transport system in liver and tumor mitochondria are similar, the resistance of tumor mitochondria to uncoupling by Ca^{2+} must involve factors other than the entry of Ca^{2+} into the mitochondria.

3544 INDUCTION OF GROWTH IN RESTING FIBROBLASTIC CELL CULTURES BY CA^{++}. (Eng.) Dulbecco, R. (Imp. Cancer Res. Fund Lab., London, England); Elkington J. *Proc. Natl. Acad. Sci. USA.* 72(4):1584-1588; 1975.

Resting cultures of BALB/c 3T3 cells were studied for their response to the addition of a complete vitamin mixture, a phosphate mixture, KCl, $MgCl_2$, or $CaCl_2$. Radioautographs were carried out after labeling the treated cultures with ^{3}H-thymidine. Only the addition of $CaCl_2$ induced DNA replication. The effect was present even in a serum-free medium. In-

creasing the Ca^{++} concentration above the standard 1.8 mM in the medium of a new culture increased the total number of cells ultimately produced, without affecting the initial cell growth rate. This effect was synergistic with that of serum. The elevated Ca^{++} concentration also induced striking morphological changes. The cells were elongated, highly refractile, and criss-crossed each other. The Ca^{++} effect could not be reproduced by a Ca^{++} ionophore. These observations afford a new tool for studying how the various intracellular events following the addition of growth factors to resting cultures are involved in the control of cellular growth.

3545 DIRECT MEASUREMENT OF THE MEMBRANE POTENTIAL OF EHRLICH ASCITES TUMOR CELLS: LACK OF EFFECT OF VALINOMYCIN AND OUABAIN. (Eng.) Smith, T. C. (Univ. Texas Health Science Center, San Antonio, Tex. 78284); Levinson, C. *J. Membr. Biol.* 23(3/4):349-365; 1975.

The membrane potential of Ehrlich ascites tumor cells and the effects of valinomycin and ouabain upon it were investigated. Membrane potential measurements were made using Ling-Gerard glass microelectrodes filled with 3 M KCl. The membrane potential in control cells was 12.0 mV, inside negative. Neither valinomycin (10.9 μM) nor ouabain (1mM) alone affected this value. However, valinomycin and ouabain in combination resulted in a slight hyperpolarization of the membrane. Concomitant determinations of cellular Na^+, and Cl^- showed that valinomycin induced net losses of K^+ and C^- and a net gain in Na^+ when compared to ouabain-inhibited cells. K^+ permeability was increased by approximately 30% in the presence of valinomycin. Valinomycin also caused a rapid depletion of cellular ATP. Inhibition of Na/K transport by ouabain was without sparing effect on the rate of ATP depletion. Possible mechanisms for the electroneutral increase in K^+ permeability induced by valinomycin are discussed.

3546 CELL-TO-CELL BINDING INDUCED BY DIFFERENT LECTINS. (Eng.) Rutishauser, U. (Dept. Genetics, Weizmann Inst. Sci., Rehovot, Israel); Sachs, L. *J. Cell Biol.* 65(2):247-257; 1975.

The cell-to-cell binding induced by concanavalin A (Con A) and the lectins from wheat germ, soybean, and waxbean was analyzed by measuring the ability of single cells to bind to lectin-coated cells immobilized on nylon fibers. The cells used included: (1) YAC lymphoma (L) cells obtained from a Moloney virus-induced lymphoma grown in A strain mice, (2) clone J_1 IR^-D^- myeloid leukemia cells (M) from SJL mice and two myeloid leukemia clones from SL mice, and (3) normal fibroblasts obtained from secondary cultures of golden hamster embryos. The cell-to-cell binding assay consisted of binding of cells to Con A-derivatized fibers by incubation in phosphate-buffered saline; binding of lectin to either the fiber-bound cells or free cells; and incubation of fiber-bound cells with free cells in suspension. With all lectins, cell-to-cell binding was inhibited if both cells were prefixed with 3% glutaraldehyde. However, in most cases cell-to-cell binding was enhanced when only the lectin-coated cell was prefixed. Neuraminidase (5 μg/ml, 30 min, 22 C) increased cell-to-cell binding only if both cells were treated. Although cell-to-cell binding induced by the lectins from soybean and wheat germ could be partially reversed by the appropriate competitive saccharide inhibitor, binding induced by Con A could not be reversed. The results indicate that cell-to-cell binding induced by a lectin can be prevented by an insufficient density of receptors for the lectin, insufficient receptor mobility, or induced clustering of receptors. This suggests that cell-to-cell binding induced by different lectins with a variety of cell types is initiated by a mechanism involving the alignment of complementary receptors on the colliding cells for the formation of multiple cell-to-lectin-to-cell bridges.

3547 GROWTH-DEPENDENT ALTERATIONS IN OLIGOMANNOSYL CORES OF GLYCOPEPTIDES. (Eng.) Ceccarini, C. (Dept. Biological Sciences, Hunter Coll. CUNY, New York, N.Y.); Muramatsu, T.; Tsang, J.; Atkinson, P. H. *Proc. Natl. Acad. Sci. USA* 72(8): 3139-3143: 1975.

In order to study growth-dependent pattern changes of glycopeptides, radioactive mannose was used as a precursor to label the surface glycopeptides of growing and nongrowing human diploid cells (KL-2). The glycopeptides were separated into neutral glycopeptides and acidic glycopeptides by paper electrophoresis. Growth-dependent alterations occurred in oligomannosyl cores in the neutral glycopeptides; namely, the neutral glycopeptides from the surface of growing cells were more resistant to endo-β-*N*-acetylglucosaminidase D but were more susceptible to α-mannosidase (EC 3.2.1.24; α-D-mannose mannohydrolase) than those derived from the surface of nongrowing cells. Another growth-dependent change was found when the endoglycosidase-resistant material from acidic glycopeptides was compared by paper electrophoresis at pH 1.9. The material from the surface of nongrowing cells contained a component that was absent or greatly reduced in growing cells. The surface material from growing cells may be enriched in glycopeptides with complex and exposed oligomannosyl cores such as the majority of those found in ovalbumin glycopeptides.

3548 NUCLEAR PROTEIN CHANGES IN RAT HEPATOMAS CORRELATING WITH GROWTH RATE. (Eng.) Lea, M. A. (New Jersey Medical Sch., Newark, N. J. 07103); Koch, M. R.; Morris, H. P. *Cancer Res.* 35(7):1693-1697; 1975.

The nature of nuclear proteins that are soluble in 8 M urea-50 mM phosphate, pH 7.6, was compared in rat liver and Morris hepatomas to examine any progressive changes that correlate with the growth rate of the tumors. Hepatomas were transplanted bilaterally sc in male Buffalo rats. Partial hepatectomies involved the removal of approximately 66% of the liver. For isoelectric focusing in polyacrylamide gels, the gels contained 200 μg protein in a total volume of 2 ml. The pH gradient was measured by pH determinations of 2-ml aqueous extracts of 4-mm gel slices. Polyacrylamide gel electrophoresis in 6.25 M urea-0.9 M acetic acid was used for separation of histones. Isoelectric focusing, using

carrier ampholytes for a pH gradient of 3.5-10, indicated that with increasing growth rate of the hepatomas there was a progressive tendency for a decrease in nonhistone nuclear proteins with isoelectric points in the range 7.5-8.9 and an increase in the range 5.1-6.7. Studies on the influence of time on the pH gradient revealed that a nonuniform drift provided a better resolution of the pH range 7.5-8.9 at seven hours than at 24 hr; the latter time for electrofocusing gave an improved resolution of the pH range 5.1-6.7. Polyacrylamide gel electrophoresis showed that 8 M urea-50 mM phosphate, pH 7.6, extracted a small part of the histones from nuclei of both liver and hepatomas. There was less extraction of histones from the hepatoma nuclei, especially in two rapidly growing hepatomas, with the most notable difference being seen in the lysine-rich H1 histone. The results suggest that in addition to qualitative or quantitative changes in nonhistone nuclear proteins in liver cancer there are alterations in the binding of histones to chromatin.

3549 CHARACTERIZATION OF R-TYPE VITAMIN B_{12}-BINDING PROTEINS BY ISOELECTRIC FOCUSING. III. COBALOPHILIN (R PROTEIN) IN MYELOPROLIFERATIVE STATES AND LEUKOCYTOSIS. (Eng.) Stenman, U.-H. (The Minerva Foundation Inst. Medical Res., P. O. Box 819, SF-00101 Helsinki 10, Finland). *Scand. J. Clin. Lab. Invest.* 35(2):157-161; 1975.

The R-type vitamin B_{12}-binding protein (cobalophilin) in plasma and serum of patients with myeloproliferative diseases and leukocytosis was studied by gel filtration and isoelectric focusing. The isoproteins composing the cobalophilin were mainly the same in these disorders as in plasma of five healthy subjects. In 6 of 12 patients with chronic myelogenous leukemia and 2 of 14 patients with leukocytosis some of the isoproteins were more acid than those found in healthy subjects. In chronic myelogenous leukemia, the high unsaturated vitamin B_{12}-binding capacity of plasma was due to an increase in the fairly acid isoproteins, whereas in polycythemia vera and in most cases of leukocytosis there was an increase in the least acid isoproteins.

3550 COMPARISON OF GLUCOCORTICOID-BINDING PROTEINS IN NORMAL AND NEOPLASTIC MAMMARY TISSUES OF THE RAT. (Eng.) Goral, J. E. (Univ. of Rochester Sch. of Medicine and Dentistry, Rochester, N.Y.); Wittliff, J. L. *Biochemistry* 14(13):2944-2952; 1975.

Kinetic and molecular properties of components binding (^{3}H)triamcinolone acetonide were studied using 105,000 x *g* supernatants of lactating mammary gland, R3230AC, and dimethylbenz(*a*)anthracene (DMBA) induced mammary tumors of the rat. The relationship between specific glucocorticoid binding and protein concentration was linear in the range of 0.5-4.0 mg protein/reaction. These cytoplasmic macromolecules bound (^{3}H)triamcinolone acetonide with limited capacity (50-400 fmole/mg of cytosol protein) and high affinity, K_d about 10^{-8}-10^{-9} M. Association of ^{3}H-triamcinolone acetonide and its binding sites was maximal by 6-8 hr at 3 C and remained unchanged up to 24 hr. The rate constant of association at 3 C was 2 to 4 x 10^5/M/min. Estimation of the half-life of the steroid-binding protein complexes from the K_d an the rate constant for association gave a value of 11 12 hr. The glucocorticoids, triamcinolone acetonide corticosterone, cortisol, and dexamethasone competed well for (^{3}H)triamcinolone acetonide binding sites. Progesterone, aldosterone, and the anti-glucocorticoid, cortexolone, were also good competitors while androgens and estrogens were weak inhibitors of binding. The binding components sedimented at 7-8S in sucrose gradients of low ionic strength and dissociated into lower molecular components sedimenting a 4-5S in high ionic strength gradients. Studies usin Sprague-Dawley female rats bearing the DMBA-induced tumor demonstrated that (^{3}H)triamcinolone acetonide binding complexes were present in cytoplasmic and nuclear compartments. Sedimentation coefficients of th cytoplasmic and nuclear forms of these receptors labeled *in vivo* were 7-8S and 4S, respectively. These studies suggest that the molecular and kinetic binding properties of glucocorticoid receptors are similar in neoplastic and normal mammary gland.

3551 EFFECT OF CHEMICAL INACTIVATING AGENTS ON GLUCOCORTICOID RECEPTOR PROTEINS IN MOUSE AND HAMSTER CELLS. (Eng.) Young, H. A. (Natl. Cancer Inst., Bethesda, Md. 20014); Parks, W. P.; Scolnick, E. M. *Proc. Natl. Acad. Sci. USA* 72(8):3060-3064; 1975.

The effects of chemicals which inactivate the binding capacity of the cytoplasmic receptor protein for [^{3}H]glucocorticoid hormones were studied. Treatment of mouse (cell line C3H MT Cl 101) or baby hamster kidney cell (BHK) (lacking thymidine kinase) cytosol with N-ethylmaleimide or iodoacetamide rapidly inactivated the [^{3}H]glucocorticoid hormone binding activity of either cytosol. Prebinding the glucocorticoid hormone, dexamethasone, to the cytosol receptor blocked the rapid inactivation of the receptor by N-ethylmaleimide. Treatment of the prebound hormone-receptor complex with iodoacetamide prevented the subsequent binding of the hormone-receptor complex to DNA without causing a dissociation of the complex. Although interpretation of the results is complicated because crude extracts were used, the results suggest that a sulfhydryl group is involved in the binding of glucocorticoid hormones to the receptor protein. It appears that iodoacetamide inactivates a separate chemical site which is necessary for the binding of the hormone-receptor complex to DNA.

3552 THE CONTROL OF PROTEIN SYNTHESIS DURING THE STIMULATION OF LYMPHOCYTES BY PHYTOHAEMAGGLUTININ. III. POLY(U) TRANSLATION AND THE RATE OF POLYPEPTIDE CHAIN ELONGATION. (Eng.) Kay, J. E. (Sch. Biol. Sci., Univ. Sussex, Brighton, England); Ahern, T.; Lindsay, V. J.; Sampson, J. *Biochim. Biophys. Acta* 378(2):241-250; 1975.

Cell-free systems prepared from pig lymphocytes stimulated by phytohemagglutinin (PHA) were studied to determine the effect of PHA stimulation on translation and polypeptide chain elongation. Lymphocytes

were purified from defibrinated pig blood by column chromatography and centrifugation, and resuspended in Eagle's minimal essential medium with 50 U of penicillin and 50 μg streptomycin/ml. Purified PHA was added and cultures were incubated for 20-24 hr at 37 C. The cells were collected by centrifugation and resuspended, then lysed and centrifuged at 10,000 x *g* for 10 min. The supernatant (S-10) was equilibrated with 80 mM KCl, 25 mM Tris HCl buffer, pH 7.6, 4 mM Mg acetate, 6 mM mercaptoethanol along a Sephadex column to form the protein-synthesizing system. tRNA was prepared from rabbit reticulocyte cell sap by extraction with phenol and precipitation with ethanol; it was then resuspended in water. S-10 from stimulated lymphocytes incorporated 3 counts/min (CPM)/1,000 μg RNA of ^{35}S-methionine in 10 min *versus* 0.5 CPM/1,000 μg RNA by S-10 from unstimulated lymphocytes. Addition of reticulocyte tRNA reduced the ratio of incorporation of ^{14}C-phenylalanine by stimulated and unstimulated S-10 from 8, with no tRNA added, to 2, with 2 μg tRNA. When 1.7×10^{-4} M sparsomysin was added to the S-10, formation of phenylalanyl-tRNA by unstimulated S-10 was 25-60% that of stimulated S-10. Addition of tRNA abolished this difference; 2,548 CPM/μg S-10 RNA (unstimulated) *versus* 2,204 CPM/μg S-10 RNA (stimulated). The rate of polypeptide chain elongation was determined using the rate of ^{14}C-leucine uptake by S-10 and the difference (0.7 min) was considered insignificant. It is concluded that cell-free systems from PHA-stimulated pig lymphocytes are more active in protein synthesis than unstimulated systems, and that tRNA added to the systems abolishes this difference. Since the rate of chain elongation is unaffected by stimulation, it appears that the increased rate of synthesis results from increased frequency of initiation of synthesis.

3553 NUCLEOLAR PHOSPHOPROTEINS OF NORMAL RAT LIVER AND NOVIKOFF HEPATOMA ASCITES CELLS. (Eng.) Kang, Y. J. (Baylor Coll. Medicine, Houston, Tex.); Olson, M. O. J.; Jones, C.; Busch, H. *Cancer Res.* 35(6):1470-1475; 1975.

Liver cells from normal albino rats (high rate of nucleolar synthesis) and rats with Novikoff hepatoma (low rate of nucleolar synthesis) were studied to determine any differences in phosphylation of nucleolar proteins in the two types of tissue. The nucleolar acid-soluble proteins from normal liver and Novikoff hepatoma ascites cells were labeled *in vivo* for two hours after the injection of [^{32}P]orthophosphate and *in vitro* with [γ-^{32}]ATP in systems containing 0.25 M sucrose, 5 mM $MgCl_2$, 12.5 mM NaCl, and 0.05 M Tris-HCl buffer, pH 7.3 at 37 C. Two-dimensional polyacrylamide gel electrophoresis and autoradiography showed that approximately 40 and 20 protein spots were labeled *in vivo* and *in vitro*, respectively. There were some marked differences in labeling *in vivo* between normal rat liver and Novikoff hepatoma acid-soluble nucleolar proteins. By ^{32}P analysis of gel slices, the proportion of the total ^{32}P incorporated into protein Spot A1-4 was greater in normal liver, and the proportion of ^{32}P incorporated into some high-molecular-weight protein spots, such as C23-4 and C26-27, was greater in the Novikoff hepatoma ascites cells. With the *in vitro* incubation system, the ^{32}P uptake per mg protein was about twice as high in Novikoff hepatoma nucleolar proteins as in normal rat liver nucleolar proteins, but, generally, the same proteins were labeled in both tissues. The results indicate that certain nucleolar proteins from both tissues differ *in vitro* and *in vivo* with respect to ^{32}P incorporation. It is suggested that highly labeled Spot A1-4 of normal liver may be the AL(2A, f2a2) histone or a nonhistone protein of low molecular weight.

3554 INITIATION FACTORS IN PROTEIN SYNTHESIS BY FREE AND MEMBRANE-BOUND POLYRIBOSOMES OF LIVER AND HEPATOMA. (Eng.) Murty, C. N. (Univ. South Florida, Coll. Medicine, Tampa, Fla. 33620); Verney, E.; Sidransky, H. *Biochem. J.* 152(1):143-151; 1975.

The activity of initiation factors obtained from free and membrane-bound polyribosomes of liver and of transplantable H5123 Morris hepatoma of rats was investigated by poly(U)-directed polyphenylalanine synthesis. Initiation factors of membrane-bound polyribosomes prepared with deoxycholate exhibited 50-75% less activity in incorporating [^{14}C]phenylalanyltRNA into polypeptides than did initiation factors of free polyribosomes. However, when membrane-bound polyribosomes were prepared after using Triton X-100, no significant differences in activities were observed between the initiation factors of free and membrane-bound polyribosomes. These results suggest that Triton X-100 is preferable to deoxycholate in the isolation of initiation factors from polyribosomes. Initiation factors, prepared by using Triton X-100, of free polyribosomes of hepatoma exhibited greater activity in the stimulation of polyphenylalanine synthesis than did the initiation factors of free or membrane-bound polyribosomes of host livers or of membrane-bound polyribosomes of hepatomas.

3555 ISOLATION OF RABBIT RETICULOCYTE INITIATION FACTORS BY MEANS OF HEPARIN BOUND TO SEPHAROSE. (Eng.) Waldman, A. A. (New York Blood Center, New York, N.Y. 10021): Marx, G.; Goldstein*, J. *Proc. Nat. Acad. Sci. USA* 72(6):2352-2356; 1975.

Cell-free extracts of New Zealand white rabbit reticulocytes were passed through a heparin-Sepharose column to confirm the interaction of heparin and initiation factors. Fraction C, 0.8% of the applied protein, was recovered from the columns by increasing the KCl concentration of the eluting buffer from 0.12 M to 0.5 M. The initiation factor activity of the bound protein equaled that of a crude initiation fraction preparation obtained from rabbit reticulocyte ribosomes. In the presence and absence of added rabbit globin messenger RNA (mRNA), fraction C was assayed for its ability to stimulate protein synthesis in a preincubated krebs ascites cell-free system. Fraction C did not stimulate protein synthesis in the absence of added mRNA; however, in the presence of added globin mRNA, addition of fraction C markedly stimulated L-[^{3}H]leucine incorporation into protein. The initiation factor activity of fraction C was confirmed in a fractionated cell-free system. The protein pattern of the fraction elec-

trophoresed on polyacrylamide gels differed sharply from the parent reticulocyte S-30, but was similar to the pattern of crude initiation factor. Addition of either heparin or aurin tricarboxylic acid (ATA) to assay mixtures containing untreated reticulocyte S-30 or reticulocyte S-30 passed through a control column decreased protein synthesis. Protein synthesis of assay mixtures containing reticulocyte S-30 that passed through a heparin-Sepharose column was unaffected by the presence of heparin or ATA, indicating that the L-[^{3}H]leucine incorporation observed with this extract represented only elongation and termination of protein chains. Thus, by inhibition of initiation, the level of protein synthesis in both the untreated and control column pass-through S-30 could be reduced to that of the heparin column pass-through S-30. Addition of fraction C resulted in a restoration of protein synthesis in the heparin column pass-through S-30 to that of the untreated S-30. The authors suggest that heparin-Sepharose chromatography simplifies the preparation of initiation factors.

3556 SOME PROPERTIES OF A DNA-UNWINDING PROTEIN UNIQUE TO LYMPHOCYTES FROM CHRONIC LYMPHOCYTIC LEUKEMIA. (Eng.) Huang, A. T. F. (Duke Univ. Med. Cent., Durham, N.C.); Riddle, M. M.; Koons, L. S. *Cancer Res.* 35(4):981-986; 1975.

Lymphocytes from a common human leukemia, chronic lymphocytic leukemia, have a greatly enhanced capability of DNA repair and a concomitantly prolonged survival *in vitro* after damage to DNA. A DNA-binding protein with a molecular wt of 24,000 was isolated and purified from lymphocytes of four patients with chronic lymphocytic leukemia. The purification process involved passing crude cell homogenates twice through a double-stranded DNA column and rechromatographing the flow-through in a UV-irradiated DNA cellulose column. The protein binds tightly to both UV-irradiated and single-stranded DNA. At 35° it enhances the helix-coil transition of poly[d(A-T)] and the UV-irradiated calf thymus DNA but is inefficient in ordinary native DNA. This protein also facilitates the rate of UV-endonuclease incision of UV DNA but does not induce any nicks by itself. This finding suggests that the protein may be involved in DNA repair by enhancing such activity, and also offers an explanation for the increased DNA repair observed in chronic lymphocytic leukemia cells. When human metaphase chromosomes are exposed to the protein, it induces marked lengthening of chromatids suggesting that this protein may also act on complex chromosomes. By quantitative immunochemical determinations, such protein could not be found in lymphocyte extracts of three normal individuals.

3557 PUTRESCINE, SPERMIDINE, N-ACETYLSPERMIDINE AND SPERMINE IN THE URINE OF PATIENTS WITH LEUKEMIAS AND TUMORS. (Eng.) Tsuji, M. (Osaka Univ. Med. Sch., Japan); Nakajima, T.; and Sano, I. *Clin. Chim. Acta* 59(2):161-167; 1975.

N-acetylspermidine A and *N*-acetylspermidine B were isolated from human urine containing 120 g of creatinine by ion exchange chromatography. Structures of the isolated compounds were assigned to monoacetylspermidines by analyses of the products of acid hydrolysis. The identification was confirmed by comparison of the chromatographic and electrophoretic properties and infrared spectra of the isolated compounds with those of the authentic compounds. The concentrations of urinary polyamines were determined by a combination of ion-exchange chromatography and high-voltage paper electrophoresis. The amount of putrescine fell in the range of 1-6 nm/mg creatinine, spermidine, 1-3 nm/mg; spermine, 3-15 nm/mg creatinine, and *N*-acetylspermidines, 2-10 nm/mg creatinine for both sexes and different ages. The amounts of urinary polyamines were measured in patients with chronic leukemia (four), reticulocyte sarcoma (one), reticulum cell sarcoma (five), multiple myeloma (one), cranio-pharyngioma (one), breast cancer (one), maxillary cancer (one), osteosarcoma (two), and stomach cancer (two). The amount of spermine increased considerably in the urine of patients with blood cancer, while the increase of the amounts of putrescine and spermidine as well as *N*-acetylspermidines was less. In the other solid tumors, no remarkable changes were observed in the pattern of urinary excretion of polyamines. It is suggested that the pattern of urinary polyamine excretion may reflect that of blood polyamines in patients with blood cancer, and that the amount of urinary spermine may be one of the indicators of therapeutic effects on blood cancer; some patients who were in remission by radiation therapy excreted amounts of spermine in the normal range.

3558 INHIBITION OF PEPTIDE CHAIN INITIATION BY A NONHEMIN-REGULATED TRANSLATIONAL REPRESSOR FROM FRIEND LEUKEMIA CELLS. (Eng.) Cimadevilla, J. M. (Dept. Chemistry, Univ. Texas at Austin, Austin, Tex. 78712); Kramer, G.; Pinphanichakarn, P.; Konecki, D.; Hardesty, B. *Arch. Biochem. Biophys.* 171(1):145-153; 1975.

Evidence that the Friend leukemia cell (FLC) translational repressor specifically inhibits initiation of natural messenger RNA (mRNA) translation without effect on peptide chain elongation or release is presented. A nonhemin-regulated translational repressor protein was partially purified from the postribosomal supernatant fraction of FLC grown in the absence of dimethylsulfoxide. This repressor inhibited protein synthesis in lysates from rabbit reticulocytes or Friend leukemia cells and in a fractionated system using *Artemia salina* ribosomes, reticulocyte mRNA, and soluble components from reticulocytes. In contrast, the hemin-controlled repressor from reticulocytes did not inhibit protein synthesis in lysates from Friend leukemia cells. The repressor from Friend leukemia cells had no effect on poly(U)-directed synthesis of polyphenylalanine using reticulocyte ribosomes or on the extension and release of nascent globin chains that were initiated in intact reticulocytes. It did not block completion of peptides on ribosomes isolated from reticulocytes incubated with NaF (10 mM), and did not inhibit initiation factor-dependent formation of methionylpuromycin; however, it did inhibit globin mRNA-dependent methionylvaline synthesis. The Friend leukemia cell repressor promoted as peptide synthesis-dependent breakdown of polysomes in

eticulocyte lysates that appeared to involve nhibition of ribosome reattachment to mRNA during eptide chain initiation. It is concluded that he FLC repressor blocks peptide initiation at a oint between the addition of methionyl-transfer-NA^{fMet} to the ribosomal initiation complex and the aF-sensitive reaction.

559 DNA SYNTHESIS IN ISOLATED HeLa CELL NUCLEI. EVIDENCE FOR *IN VITRO* INITIATION F SYNTHESIS OF SMALL PIECES OF DNA AND THEIR SUBEQUENT LIGATION. (Eng.) Krokan, H. (Inst. Medical iology, Univ. Tromso, 9000 Tromso, Norway); Cooke, .; Prydz*, H. *Biochemistry* 14(19):4233-4237; 1975.

NA synthesis in isolated HeLa cell nuclei was tudied. Fresh nuclei isolated from synchronized ells were preincubated in a test mixture containing o nucleotides and were then pulse-labeled by addiion of a nucleotide mixture containing [^{3}H]TTP. he incubation was terminated by the addition of lkaline lysis buffer and the lysates were centriuged in alkaline sucrose gradients in which ^{14}C-abeled coliphage P2 DNA was used as a marker; [^{3}H]-TP incorporation was then assayed. The study was epeated at 22-40 and pulse-chase experiments were erformed to determine whether the ligation of priary DNA pieces takes place in isolated nuclei. uring the pulse experiments, low molecular wt ingle-stranded DNA pieces were synthesized in isoated nuclei, the size of the pieces increasing with he pulse length: when isolated nuclei were pulseabeled for 30 sec at 22 or 27 C, about 80% of the adioactivity appeared in 2-4S primary DNA pieces; nd the size increased to about 14S when the pulse ength increased to 480 sec. When the pulse time ncreased, a decreasing portion of the total label ncorporated into DNA was found in the primary DNA ieces. The primary 2-4S DNA pieces were highly Nase-sensitive. The pulse-chase experiments indiated that primary DNA pieces were ligated to fragents generally larger than 30S; no evidence was ound for discrete classes of intermediate-sized ieces between the primary and secondary DNA pieces. onreplicating DNA was much larger in the secondary ieces. Most of the label incorporated during the irst 20 sec in the pulse-chase experiments disapeared from the primary pieces within 130 sec, and he evidence indicated that the initiation of priary DNA pieces took place after that period. The esults indicate that the synthesis of DNA is disontinuous in both the 5' to 3' and 3' to 5' direcions and that primary DNA pieces are initiated *n vitro*.

560 RAT HEPATOMA CELLS NUCLEOLAR DNA. I. ANALYSIS OF NUCLEOLAR DNA. (Eng.) Amalc, F. (Centre de Recherches de Biochimie et de enetique Cellulaires, 118 Route de Narbonne, 31077 oulouse-Cedex, France); Zalta, J. P. *Nucleic Acids es.* 2(8):1305-1320; 1975.

he analysis by CsCl density gradient of Zajdela rat epatoma nucleolar DNA showed that the 1.700 g/cm^3 ain component can be subdivided in three subcompoents with buoyant densities of 1.707 g/cm^3, 700 g/cm^3, 1.690 g/cm^3. The 1.707 g/cm^3 and 1.690 g/cm components contain all the repetitive sequences which comprise 15% of the total nucleolar DNA. The ribosomal cistrons are found in components having buoyant density between 1.707 g/cm^3 and 1.725 g/cm^3. Sodium-p-aminosalicylate-DNA interactions showed that only the 1.700 g/cm^3 fraction has a destabilized secondary structure. The results suggest that the sequences with buoyant densities of 1.707 and 1.690 g/cm^3 are localized in the high molecular weight DNA of intranucleolar chromatin. The 1.700 g/cm^3 fraction contains perinucleolar chromatin.

3561 DAMAGED DNA IN LYMPHOCYTES OF APLASTIC ANEMIA. (Eng.) Hashimoto, Y. (Third Dept. Internal Medicine, Faculty Medicine, Univ. Tokyo, Tokyo, Japan 113); Takaku, F.; Kosaka, K. *Blood* 46(5):735-742; 1975.

The size of single-stranded DNA in lymphocytes in G_0 stage from 22 patients with acquired primary and secondary aplastic anemia was estimated by alkaline sucrose gradient centrifugation. The average size was 9.3 x 10^7 daltons *vs* 1.23 x 10^8 daltons for normal persons. The lymphocytes of patients contained significantly more single-strand breaks in DNA, compared with those of normal persons. The difference in size of single-stranded DNA which had been present in nontransformed lymphocytes could also be observed in transformed lymphocytes. Some characteristic differences could be observed in the sedimentation patterns of single-stranded DNA in the lymphocytes of patients with aplastic anemia and those of normal persons. For normal persons, a single main peak was seen in fraction 11 or 12 in each sedimentation profile; neither a shoulder nor an accessory peak was observed. In patients with aplastic anemia, the main peak was slightly shifted to the right; and a definite shoulder was seen in two cases. The single-strand breaks in DNA suggested that the repair processes were disturbed in the DNA molecules of circulating lymphocytes from patients with acquired primary and secondary aplastic anemia.

3562 DNA CONTENT OF MOUSE HEPATOMA NUCLEI DETERMINED BY FEULGEN CYTOPHOTOMETRY. (Eng.) Enesco, H. E. (Dept. Biological Sciences Sir George Williams Univ., Montreal, Quebec H3G 1M8, Canada); Aczel, J. *Neoplasma* 22(4):391-394; 1975.

The nuclear DNA content of hepatomas (Jax Code BW7756) transplanted sc into C57L/J mice was determined by Feulgen cytophotometry. The average amount of DNA/nucleus expressed in arbitrary units (AU) was 200.30, 407.70, and 810.00 AU for normal 2N, 4N and 8N hepatic cells, respectively. This series of DNA values gave points of comparison for the DNA values in hepatoma cell nuclei. The DNA/hepatoma cell nucleus was 302-1830 AU with an average of 825.93 $\pm$ 117.20 AU. About 30% of the hepatoma cells were in the hypertetraploid category, another 30% were in the octaploid and hyperoctaploid range, and the rest (except a few which could be considered tetraploid) exhibited a greater degree of polyploidy and aneuploidy, some in the

16N range and higher. Feulgen cytophotometric results showed that the average amount of DNA in the hepatoma cell nuclei was at the octaploid level. The hepatoma nuclei showed a wide range of variation from cell to cell, indicating that the hepatoma cell population is both polyploid and aneuploid.

3563 THE RELATIVE UTILIZATION OF THE ACYL DIHYDROXYACETONE PHOSPHATE AND GLYCEROL PHOSPHATE PATHWAYS FOR SYNTHESIS OF GLYCEROLIPIDS IN VARIOUS TUMORS AND NORMAL TISSUES. (Eng.) Pollock, R. J. (Ment. Health Res. Inst., Univ. Michigan, Ann Arbor); Hajra, A. K.; Agranoff, B. W. *Biochim. Biophys. Acta* 380(3):421-435; 1975.

Rates of phosphatidate synthesis from dihydroxyacetone phosphate *via* acyl dihydroxyacetone phosphate or glycerol phosphate were compared in homogenates of 13 tissues, most of which were deficient in glycerol phosphate dehydrogenase. Sources of the tissue homogenates included nitrosourea-transformed rat astroglia, simian virus 40-transformed and normal astroglia from Syrian hamsters, neuroblastoma (C1300) cells from A/J mice, splenic leukocytes from leukemic and normal C58/wm mice, lymphocytes from human peripheral blood. Sprague-Dawley rat thymocytes, male Swiss mice brain and liver, and fetal brain from a Sprague-Dawley rat. In all tissues examined, dihydroxyacetone phosphate entered phosphatidate more rapidly *via* acyl dihydroxyacetone phosphate than *via* glycerol phosphate. Tissues with a relatively low rate of phosphatidate synthesis *via* glycerol phosphate showed no compensating increase in the rate of synthesis via acyl dihydroxyacetone phosphate. The rates at which tissue homogenates synthesize phosphatidate from dihydroxyacetone phosphate via glycerol phosphate increase as glycerol phosphate dehydrogenase increases. Both glycerol phosphate dehydrogenase and glycerol phosphate:acyl coenzyme A (CoA) acyltransferase are more active than dihydroxyacetone phosphate:acyl CoA acyltransferase. Thus, all the tissue homogenates possessed an apparently greater capability to synthesize phosphatidate via glycerol phosphate than via acyl dihydroxyacetone phosphate, but did not express this potential. This result is discussed in relation to *in vivo* substrate limitations.

3564 COMPARATIVE ADENYLATE CYCLASE ACTIVITIES IN HOMOGENATE AND PLASMA MEMBRANE FRACTIONS OF MORRIS HEPATOMA 5123tc (h). (Eng.) Hickie, R. A. (Univ. Saskatchewan, Saskatoon, Canada); Jan, S. H.; Datta, A. *Cancer Res.* 35(3):596-600; 1975.

Homogenate and plasma membrane fractions of Morris hepatoma 5123tc(h) and Buffalo rat liver were studied with regard to their relative basal activities of adenylate cyclase and to the comparative responsiveness of this enzyme to glucagon, sodium fluoride, epinephrine, prostaglandin E_1, and insulin. The basal adenylate cyclase activities of the hepatoma fractions were similar to those of liver at an ATP concentration of 3.2 mM; if the substrate affinity (K_m-ATP) of the tumor enzyme is comparable to that of liver, these findings suggest that the reduced basal cyclic AMP levels found to occur in hepatoma 5123tc(h) probably are not due to a decreased basal rate of formation of this cyclic nucleotide. Glucagon (5.6 μM) significantly stimulated adenylate cyclase in both fractions of hepatoma and liver; however, the responsiveness of the tumor enzyme to this hormone was substantially lower than the responsiveness of liver for both homogenate and plasma membrane preparations; i.e., activities were enhanced 18-fold (relative to the basal activity) for liver homogenate compared with only a six-fold increase for tumor. With the plasma membrane preparations, glucagon increased the activities 5- and 3.5-fold in liver and hepatoma, respectively. Sodium fluoride (10 mM), in contrast to glucagon, increased the adenylate cyclase activity to approximately the same extent (about 10-fold) in the liver and hepatoma preparations. Epinephrine (100 μM) enhanced the liver and hepatoma homogenate activities 3- to 4-fold and the hepatoma plasma membrane activities two-fold: however, the liver plasma membrane activities were not increased. Prostaglandin E_1 (56.6 μM) significantly increased adenylate cyclase activities of liver and hepatoma homogenates (i.e., 1.5- and 3-fold, respectively) but not of the plasma membrane preparations. Insulin (0.7 μM) did not significantly alter adenylate cyclase activities in any of the preparations.

3565 INCREASED ACTIVITY OF LOW-K_m CYCLIC ADENOSINE 3':5'-MONOPHOSPHATE PHOSPHODIESTERASE IN PLASMA MEMBRANES OF MORRIS HEPATOMA 5123tc (h). (Eng.) Hickie, R. A. (Univ. Saskatchewan, Saskatoon, Canada); Walker, C. M.; Datta, A. *Cancer Res.* 35(3);601-605; 1975.

Homogenates and plasma membranes of Morris Hepatoma 5123tc (h) tumors and rat liver were utilized to demonstrate the increased activity of Low-K_m cyclic 3':5'-AMP phosphodiesterase. Tissue homogenates were prepared in sucrose, potassium phosphate and EDTA with one half being used directly and the other half centrifuged at 10,000 x *g*. The release of P_i from cAMP was used as an indication of total cAMP phosphodiesterase activity. The "2-stage" assay method was incorporated to differentiate between low K_m and high K_m phosphodiesterase activity. Results indicated that cAMP of hepatoma homogenates and 100,000 x g supernatant fractions were lower than those of liver. There was a significant increase in low k_m cAMP phosphodiesterase activity in hepatoma plasma membranes; theophylline was found to inhibit activity. This increase is thought to be related to an increase in the metabolic rate of cAMP by low k_m phosphodiesterase in plasma membranes. Further investigation into the mechanisms by which this increase occurs in indicated.

3566 COMPARISON OF TWO ISOZYMES OF CARBONIC ANHYDRASE IN THE RAT ANTERIOR PITUITARY GLAND AND PITUITARY TUMORS. (Eng.) Kimura, H. (Univ. Virginia Sch. Med., Charlottesville); MacLeod, R. M. *Cancer Res.* 35(3):796-800; 1975.

Two isozymes of carbonic anhydrase were compared in the anterior pituitary gland of nontumor-bearing rats and in the hormone-secreting pituitary tumors. In

contrast to the pituitary gland, which contained 60 to 70% of the total carbonic anhydrase in the particulate subcellular fraction, three hormone-secreting pituitary tumors (MtTW5, MtWi5, StW5) were devoid of the particulate (Triton X-100-solubilized) enzyme activity. Another pituitary tumor, 7315a, contained particulate carbonic anhydrase, but the activity was only 45% of the activity of normal pituitary gland. During the development of the rat brain, the particulate (Triton X-100-solubilized) carbonic anhydrase activity was undetectable in preparations up to 21 days of age (body wt, 47 G). After that age, the carbonic anhydrase activity in the particulate fraction increased rapidly and reached the adult level at 37 days (body wt, 120 g), while the activity in the soluble fraction increased gradually after birth and then reached a plateau at 30 days (body wt, 81 g). These data show that the isozyme pattern of carbonic anhydrase in pituitary tumor tissue from Wistar-Furth and Buffalo rats resembles the pattern in fetal cells more than the pattern in adult tissue.

3567 MULTIPLE MOLECULAR FORMS OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE IN NORMAL, PRENEOPLASTIC, AND NEOPLASTIC MAMMARY TISSUES OF MICE. (Eng.) Hilf, R. (Univ. of Rochester Sch. of Medicine and Dentistry, Rochester, N.Y. 14642); Ickowicz, R.; Bartley, J. C.; Abraham, S. *Cancer Res.* 35(8): 2109-2116; 1975.

Multiple molecular forms of glucose-6-phosphate dehydrogenase (G6PD) in normal, preneoplastic, and neoplastic mammary tissues were separated by polyacrylamide gel electrophoresis and identified by specific staining for enzyme activity. Mammary tissue from lactating BALB/c mice showed up to 50% of a slower-migrating G6PD species, (G6PD-III) which was essentially absent from glands of pregnant mice, preneoplastic nodules, and mammary carcinomas. All tissues possessed a faster-migrating species, G6PD-II, which accounted for up to 85% of the total G6PD in the glands of pregnant mice. A third species, G6PD-I, migrating more rapidly than G6PD-II, was found in both abnormal tissues and accounted for up to 35% of the total enzymatic activity. G6PD-I was present at less than 15% in glands from pregnant mice and at about 5% in the lactating gland. The addition of dithiothreitol increased G6PD-II or G6PD-I. Stirring overnight at 4 C (in air) resulted in a loss of G6PD activity, but preparations had greater amounts of G6PD-III; presence of dithiothreitol during aeration partially prevented loss of G6PD activity and largely prevented the appearance of G6PD-III. Molecular-wt estimations with preparations from lactating mice yielded a value of 118,000 for G6PD-II and 260,000 for G6PD-III, suggesting a monomer and dimer. The addition of NADP prevented heat activation of G6PD at 47 C. The heat inactivation studies suggest that G6PD-III (dimer) was the more stable species. The activity of glutathione reductase may influence the pattern of G6PD species in different tissues.

3568 LYSOSOMAL AND MITOCHONDRIAL ENZYME ACTIVITIES IN HUMAN LYMPHOID CELL LINES OBTAINED FROM CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA AND CONTROLS. (Eng.) Sippell, W. G. (Kinderklinik der Universitat Munchen, 8 Munchen 15, BRD); Antonowicz, I.; Lazarus, H.; Shwachman, H. *Exp. Cell Res.* 91(1):152-158; 1975.

The activities of seven lysosomal and three mitochondrial enzymes from isolated lysosomes and mitochondria of cultivated lymphoid cell lines, obtained from three patients with acute lymphoblastic leukemia and from six normal individuals, were studied. The lysosomal enzymes included α-glucosidase, β-glucosidase, β-glucuronidase, β-galactosidase, aryl sulfatase, *N*-acetyl-β-glucosaminidase, and acid phosphatase. These enzymes are involved in the degradation of glycoprotein, glycolipids, mucopolysaccharide-protein complexes, polysaccharides, organic sulfates, and phosphoric esters. The mitochondrial enzymes studied were succinate dehydrogenase, glutamate dehydrogenase, and malate dehydrogenase. The specific activities of the lysosomal enzymes were markedly higher in the leukemic cell lines than in the control cell lines, with the possible exception of aryl sulfatase. No marked increase of mitochondrial enzyme activities was found in mitochondrial fractions from the leukemic cells. This study demonstrates that lymphoid cells from patients with acute lymphoblastic leukemia differ markedly from normal cells in terms of lysosomal function.

3569 HISTOCHEMICAL STUDIES OF GLYCOGEN METABOLIZING ENZYMES IN NORMAL AND ABNORMAL HUMAN CERVICAL EPITHELIUM. (Eng.) Skerlavay, M. A. (State University Hosp., Box 37, 450 Clarkson Ave., Brooklyn, N. Y. 11203); Bigelow, B.; Demopoulus, R. I. *Acta Histochem. (Jena)* 53(2):233-237; 1975.

The stratified squamous epithelium in eleven cervical cone biopsies was studied for localization of glycogen, glycogen synthetase, branching enzyme and amylophosphorylase in areas showing normal, dysplastic epithelium, and carcinoma *in situ*. In the normal cervix glycogen was present in the intermediate and superficial cells; amylophosphorylase activity was present in the basal and parabasal layers; and the branching enzyme was found largely in the lower and middle zone of the intermediate layer. As the degree of abnormality increased, a progressive decrease of glycogen and branching enzyme and increasing amylophosphorylase was found, suggesting that amylophosphorylase is a constitutive enzyme, persisting when no glycogen is found, in normal, dysplastic, and neoplastic cells. Branching enzyme was not shown in any example of severe dysplasia or carcinoma *in situ*; amylophosphorylase was present through the full thickness of the epithelium. The method for localization of glycogen synthetase activity was not reproducible.

3570 AN EVALUATION OF LYSOSOMAL ENZYME LEAKAGE AS A FACTOR INFLUENCING THE BEHAVIOUR OF TRANSFORMED CELLS. (Eng.) Elligsen, J. D. (Dept. Biology and Physics Univ. Waterloo, Waterloo, Ont., Canada N2L3G1); Thompson, J. E.; Frey, H. E. *Exp. Cell Res.* 92(1):87-94; 1975.

The extent of lysosomal enzyme leakage from normal and transformed baby hamster kidney (BHK) cells was

compared in light of knowledge of normal lysosomal contaminants of fetal calf serum. Commerically, available fetal calf serum contained substantial amounts of protease, acid phosphatase, and glycosidase activity that could be inactivated by heating serum to 70 C for 15 min. Heat inactivation had no influence on the ability of serum to support growth of polyoma-transformed BHK (pyBHK) cells and only marginally affected the growth properties of BHK cells. Glycosidases and acid phosphatase were also detectable in medium containing heat-inactivated serum and conditioned by growth of either BHK or pyBHK cells. This latter activity could be attributed solely to enzymes derived from the growing cells and, for most of the enzymes monitored, was present to a greater extent in medium conditioned by transformed cells as compared to normal cells. In all cases, however, enzyme activity derived solely from cells was only 1-10% of that indigenous to commercial tissue culture medium by virtue of its fetal calf serum component. The observation that these elevated enzyme levels accompany DNA or RNA tumor virus-mediated cell transformation indirectly supports the proposal that lysosomal enzymes may cause uncontrolled cell growth by creating architectural modifications of the cell surface.

3571 4-AMINOBUTYRATE IN MAMMALIAN PUTRESCINE CATABOLISM. (Eng.) Seiler, N. (Max-Planck-Institut fur Hirnforschung, Arbeitsgruppe Neurochemie, Frankfurt/Main, West Germany); Eichentopf, B. *Biochem. J.* 152(2):201-210; 1975.

The effects of inhibitors of diamine oxidase, monoamine oxidase and 4-aminobutyrate aminotransferase on the catabolism of putrescine in mice were studied. catabolism of putrescine in mice were studied. Diamine oxidase inhibitors (hydrazine sulfate, 60 mg/kg,ip; aminoguanidine sulfate, 60 mg/kg,ip) and 50 mg/kg carboxymethoxylamine (aminooxyacetate) markedly (100 mg/kg, 5.5 hr after administration or 50 mg/kg, 2,3, and 5 hr) the metabolism of [^{14}C] putrescine to $^{14}CO_2$ to about 2%, but they affected different enzymes. Aminoguanidine specifically inhibited the mitochondrial and non-mitochondrial diamine oxidases, whereas carboxymethoxylamine specifically inhibited 4-aminobutyrate transamination by the mitochondrial pathway. Hydrazine inhibited at both sites, and resulted in increased concentrations of 4-aminobutyrate in brain and liver. Pretreatment of mice with carboxymethoxylamine (100 mg/kg, 5.5 hr after administration or 50 mg/kg, 2,3, and 5 hr) and [^{14}C]putrescine led to the urinary excretion of amino[^{14}C]butyrate. Carboxymethoxylamine did not affect the non-mitochondrial pathway of putrescine catabolism, as the product of oxidative deamination of putrescine in the extramitochondrial compartment was not further oxidized but was excreted in the urine as derivatives of 4-aminobutyraldehyde. The monoamine oxidase inhibitor, pargyline (60 mg/kg) decreased the metabolism of [^{14}C]-putrescine to $^{14}CO_2$ *in vivo*. Catabolism of putrescine to CO_2 *in vivo* occurs along different pathways, both of which have 4-aminobutyrate as a common intermediate, in contrast with the non-mitochondrial catabolism of putrescine, which terminates in the excretion of 4-aminobutyraldehyde derivates. The significance of the different pathways is discussed.

3572 DNA-METABOLIZING ENZYMES IN NORMAL HUMAN LYMPHOID CELLS: VI. INDUCTION OF DNA POLYMERASES α, β, AND γ FOLLOWING STIMULATION WITH PHYTOHEMAGGLUTININ. (Eng.) Mayer, R. J. (Natl. Cancer Inst., Bethesda, Md. 20014); Smith, R. G.; Gallo*, R. C. *Blood* 46(4):509-518; 1975.

At least three distinct DNA polymerases, named α, β, and γ, were previously isolated from normal mammalian cells. In this study, the change of each of the polymerase activities was measured as lymphocytes entered a mitotic cycle. Aliquots of a pool of normal human blood lymphocytes were incubated with phytohemagglutinin (PHA) for 0, 24, 48, and 72 hr, respectively, and the various DNA polymerase activities were quantitated at each time point. No significant DNA polymerase activity was detected in unstimulated cells. Low levels of polymerase β were found at 24 hr. The average DNA content per cell doubled between 24 and 48 hr, and during this interval all three DNA polymerases increased to easily detectable levels. The greatest fractional increase in activity of all three polymerases was seen between 48 and 72 hr, after the average doubling of cellular DNA. It is concluded that these blood lymphocytes lack significant levels of DNA polymerases; stimulation with PHA induces all three major DNA polymerase species. In both these respects, these cells differ from other proliferating mammalian cell systems. The possible significance of this difference is discussed.

3573 TRANSPLANTATIONS OF ISOLOGOUS PROSTATIC TISSUE IN CLEARED MAMMARY FAT PADS OF BALB/c MICE AND F344 RATS. (Eng.) Edwards, W. D. (Natl. Cancer Inst., Bethesda, Md. 20014); Bates, R. R. *Transplantation* 20(4):303-307; 1975.

The survival and proliferative changes of prostatic tissue transplanted in the gland-free mammary fat-pads of BALB/c mice and F344 rats with or without exogenous testosterone stimulation was investigated. Three other organ sites were also studied: the kidney capsule and spleen of mice, and the scapular fat-pad of rats. There were four experimental groups for the mammary fat-pad transplant site: (1) female hosts (25 rats and 70 mice) with testosterone stimulation *via* testosterone propionate pellets (15 mg), (2) female hosts (25 rats and 70 mice) without testosterone stimulation, (3) male hosts (25 rats and 108 mice) with exogenous testosterone stimulation, and (4) male hosts (25 rats and 84 mice) without exogenous testosterone stimulation. Maximum survival time of prostate transplants in both kidney and spleen of male and female hosts stimulated with testosterone was nine months. The epithelium was low and irregular. There was no survival of prostate tissue in kidney or spleen of animals without testosterone stimulation. Prostate transplants survived for as long as 12 mo in the scapular fat-pads of rats, but this site was considered unfavorable for future transplants because of the difficulty in

palpation. Transplants in the mammary fat-pad of animals stimulated with endogenous or exogenous testosterone survived as long as 21 mo, at which time the remaining animals were sacrificed. Nine months after transplantation, nodules were palpable in 93% and 67% of the male and female animals, respectively, treated with testosterone and in 76% and 4% of the male and female animals, respectively, not receiving testosterone stimulation. Male hosts given exogenous testosterone showed the largest increase (74 of 108) in transplant size (greater than 0.5 cm diameter). Histologic examination revealed that the epithelial height was maintained and that exogenous testosterone stimulation resulted in increased secretory activity in the prostate transplants. The stromal connective tissue was also increased. The prolonged viability of transplants in the cleared mammary fat-pad of the mouse and rat *in vitro* suggests its use as a model system for the investigation of changes in prostate tissue implanted from an *in vitro* to an *in vivo* environment.

3574 PARTIAL PURIFICATION OF A GLUCOCORTICOID RECEPTOR. (Eng.) Failla, D. (Dept. Biochemistry and Biophysics, Univ. California, San Francisco, Calif. 94143); Tomkins, G. M.; Santi*, D. V. *Proc. Natl. Acad. Sci. USA* 72(10):3849-3852; 1975.

A simple method for purification of the glucocorticoid receptor from hepatoma tissue culture cells has been developed. The procedure, requiring 24 hr, involves adsorption of the receptor to deoxycorticosterone-derivatized agarose, elution with a glucocorticoid (e.g. dexamethasone), and gel filtration. The receptor-steroid complex is obtained in 35-40% yield and 2000-fold purified. The purified and crude receptor [1,2,4-^{3}H]triamcinolone actonide complexes have identical sedimentation coefficient in glycerol gradients. The purified complex undergoes temperature and/or salt-dependent activation and subsequent nuclear binding. Thus the receptor obtained is the receptor characterized in the crude cytosal.

3575 EFFECTS OF TWO TYPES OF DIETARY FIBRE ON FAECAL STEROID AND LIPID EXCRETION. (Eng.) Walters, R. L. (West Middlesex Hosp., Isleworth, Middlesex, England); McLean Baird, I.; Davies, P. S.; Hill, M. J.; Drasar, B. S.; Southgate, D. A. T.; Green, J.; Morgan, B. *Br. Med. J.* 2 (5970):536-538; 1975.

Fiber supplements from wheat bran and sugar cane residues (bagasse) were added to the normal diet of 24 female volunteers for 12-wk periods in a controlled metabolic study. Nine subjects were given 10.5 g of bagasse in biscuit form, and ten others were given control biscuits that were low in fiber; after the 12-wk period, the dietary regimens were crossed over for an equal period. Blood samples were taken every two weeks for plasma cholesterol and triglyceride measurements. Four stool samples were collected in each dietary period for bacterial determination. Another five subjects were given 39 g of wheat bran as biscuits in conjunction with a low-fiber diet. Stool weights and stool fat excretion increased in subjects on both dietary fibers. Bagasse increased the daily loss of acid steroids, but bran failed to affect bile acid excretion. Decreased transit time, as measured by radio-opaque pellets, occurred with bagasse without alteration in fecal flora. The raised excretion of bile acids and fatty acids failed to lower the plasma cholesterol and triglycerides after 12 wk. Thus, different fiber sources with variable components have dissimilar metabolic effects.

3576 STUDIES ON THE DIFFERENTIATION OF HUMAN AND EXPERIMENTAL GLIOMAS IN ORGAN CULTURE SYSTEMS. (Eng.) Rubinstein, L. J. (No affiliation given); Herman, M. M. *Recent Results Cancer Res.* 51:35-51; 1975.

3577 STUDY OF THE PROCESSES OF DEVELOPMENT OF MALIGNANT TUMOURS BY HYBRIDIZATION OF SOMATIC CELLS. (Rus.) Popov, A. S. (Inst. Biology of Evolution USSR Acad. Sci., Moscow, USSR). *Arkh. Patol.* 37(6):84-87; 1975.

3578 INVESTIGATION OF CHORIOCARCINOMA CLONAL CELL LINES *IN VITRO* AND CHORIOCARCINOMA TRANSPLANTS IN THE HAMSTER FOR THE SECRETION OF A THYROID-STIMULATING FACTOR. (Eng.) Ketelslegers, J.-M. (Natl. Inst. Health, Bethesda, Md.); Nisula, B. C.; Kohler, P. O. *Endocrinology* 96(3):808-810; 1975.

3579 MODIFICATION OF TUMORIGENICITY OF L1210 LEUKEMIA BY FERRIC CHLORIDE. (Eng.) Khan, A. (Wadley Inst. Molecular Medicine, 9000 Harry Hines, Dallas, Tex. 75235); Thometz, D. *Wadley Med. Bull.* 5(2):161-164; 1975.

3580 COMPARISON OF THE "CHROMATIN FRACTION II" NONHISTONE PROTEINS OF NORMAL, PHYTOHEMAGGLUTININ STIMULATED AND LEUKEMIC HUMAN LYMPHOCYTES AND MYELOCYTES [abstract]. (Eng.) Yeoman, L. C. (Baylor Coll. Med., Houston, Tex.); Seeber, S.; Taylor, C. W.; Busch, H. *Proc. Am. Assoc. Cancer Res.* 16:43; 1975.

3581 INCREASED DEGRADATION RATES OF PROTEIN SYNTHESIZED IN HEPATOMA CELLS IN THE PRESENCE OF AMINO ACID ANALOGUES. (Eng.) Knowles, S. E. (CSIRO Division of Nutritional Biochemistry, Adelaide, S.A. 5000, Australia); Gunn, J. M.; Hanson, R. W.; Ballard, F. J. *Biochem. J.* 146(3):595-600; 1975.

3582 RELATIONSHIP BETWEEN IODINATION AND THE POLYPEPTIDE CHAIN COMPOSITION OF THYROGLOBULIN. (Eng.) Haeberli, A. (Experimentelle Endokrinologie, Inselspital Bern, Switzerland); Salvatore, G.; Edelhoch, H.; Rall, J. E. *J. Biol. Chem.* 250(19):7836-7841; 1975.

3583 ACTIN ASSOCIATED WITH MEMBRANES FROM 3T3 MOUSE FIBROBLAST AND HeLa CELLS. (Eng.) Gruenstein, E. (Dept. Biol., Massachusetts Inst. Technol., Cambridge); Rich, A.; Weihing, R. R. *J. Cell Biol.* 64(1):223-234; 1975.

3584 POLYADP-RIBOSYLATION OF HeLa CELL NUCLEAR PROTEINS: RELEASE OF TEMPLATE RESTRICTION FOR DNA POLYMERASE. (Eng.) Smulson, M. (Georgetown Univ. Sch. Med. Dent., Washington, D. C.); Roberts, J.; Stark, P. *J. Biochem. (Tokyo)* 77(1):7p; 1975.

3585 CYTOCHEMICAL STUDY OF THE DYNAMICS OF THE SYNTHESIS OF RNA DETECTED IN THE METAPHASIC CHROMOSOMES OF HeLa CELLS. (Rus.) Kucheriavenko, A. A. (Inst. Human Morphology of the U.S.S.R. Acad. Medical Sciences, Moscow, U.S.S.R.). *Biull. Eksp. Biol. Med.* 79(3):94-97; 1975.

3586 STIMULATION OF DNA SYNTHESIS *IN VITRO* BY A TUMOR PROTEASE, CANCER PROCOAGULANT A (CPA) [abstract]. (Eng.) Wood, L. G. (Univ. Colorado Med. Cent., Denver); Gordon, S. G. *Clin. Res.* 23(2):137A; 1975.

3587 MICROFLUOROMETRIC COMPARISONS OF HEAT-INDUCED NUCLEAR ACRIDINE ORANGE METACHROMASIA BETWEEN NORMAL CELLS AND NEOPLASTIC CELLS FROM PRIMARY TUMORS OF DIVERSE ORIGIN. (Eng.) Alvarez, M. R. (Dept. Biol., Univ. South Florida, Tampa). *Cancer Res.* 35(1):93-98; 1975.

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3590 ALTERATIONS IN THE ISOZYME SPECTRUM AND THE ACTIVITY OF LACTATE DEHYDROGENASE IN DEVELOPMENT OF EHRLICH ASCITES TUMOR. (Rus.) Agatova, A. I. (Inst. Chemical Physics, Acad. Sciences of U.S.S.R., Moscow, U.S.S.R.). *Vopr. Med. Khim.* 21(3):276-281; 1975.

3591 FETAL-TYPE OF ISOZYMES IN CANCER. (Eng.) Schapira, F. (Institut de Pathologie Moléculaire, 24 rue du Faubourg Saint-Jacques, Paris 75014, France); Hatzfeld, A.; Weber, A. *Proc. Int. Cancer Congr. 11th.* Vol. 5 *(Surgery, Radiotherapy and Chemotherapy of Cancer).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Casinelli, N. New York, American Elsevier, 1975, pp. 318-323.

3592 ISOZYME COMPOSITION OF SOLID AND CULTURED HEPATOMAS [abstract]. (Eng.) Shatton, J. B. (Temple Univ. Sch. Med., Philadelphia, Pa.); Gunn, J. M.; Hanson, R. W.; Weinhouse, S. *Proc. Am. Assoc. Cancer Res.* 16:48; 1975.

3593 EFFECT OF POLY(ADP-RIBOSE) ON DNASES OF THE NUCLEI OF RAT LIVER AND ASCITES HEPATOMA CELLS. (Eng.) Yamada, M. (Natl. Cancer Cent. Res. Inst., Tokyo, Japan); Nagao, M.; Miwa, M.; Sugimura, T. *J. Biochem. (Tokyo)* 77(1):10p-11p; 1975.

3594 GLYOXALASE II ACTIVITY IN TUMOURS. (Eng.) Jerzykowski, T. (Silesian Medical Acad. in Katowice ul. K. Marksa 19, 41-808 Zabrze, Poland); Winter, R.; Matuszewski, W.; Szczurek, Z. *Experientia* 31(1):32-33; 1975.

3595 CYCLIC AMP-DEPENDENT AND CYCLIC GMP-DEPENDENT PROTEIN KINASES IN FAST-GROWING MORRIS HEPATOMAS [abstract]. (Eng.) Shoji, M. (Emory Univ. Sch. Medicine, Atlanta, Ga. 30322); Huguley, C. M., Jr.; Groth, D. P.; Morris, H. P.; Kuo, J. F. *IRCS Med. Sci.* 3(10/Suppl.):2; 1975.

3596 PROPERTIES OF PHOSPHOENOLYPYRUVATE CARBOXYKINASE (GUANOSINE TRIPHOSPHATE) SYNTHESIZED IN HEPATOMA CELLS IN THE PRESENCE OF AMINO ACID ANALOGUES. (Eng.) Knowles, S. E. (CSIRO, Division of Nutritional Biochemistry, Adelaide, S.A. 5000, Australia); Gunn, J. M.; Reshef, L.; Hanson, R. W.; Ballard, F. J. *Biochem. J.* 146(3):585-593; 1975.

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Volume XIII, No. 7
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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

Carcinogenesis Abstracts is normally published monthly. Volume XIII covers the scientific literature published from Jan 1975 through Dec 1975. To increase the usefulness of *Carcinogenesis Abstracts*, Volume XIII, a Wiswesser Line Notation index and a Chemical Abstracts Service Registry Number index have been provided. These indexes reference compounds described in abstracted articles. A cumulative subject, author, CAS Registry Number, and Wiswesser Line Notation index for Volume XIII will be published shortly after the final regular issue.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations found in *Chemical Abstracts Service Source Index*, 1907-1974 Cumulative, are used. New journals are verified in *New Serial Titles* and abbreviated according to *International Standard ISO 833*. An asterisk indicates the author to address (other than the primary) in requesting reprints.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	Ind.	Indonesian
Ara.	Arabic	Ita.	Italian
Bul.	Bulgarian	Jpn.	Japanese
Chi.	Chinese	Kor.	Korean
Cro.	Croation	Lav.	Latvian
Cze.	Czech	Lit.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
Eng.	English	Por.	Portuguese
Est.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fle.	Flemish	Ser.	Serbo-Croatian
Fre.	French	Slo.	Slovak
Geo.	Georgian	Spa.	Spanish
Ger.	German	Swe.	Swedish
Gre.	Greek	Tha.	Thai
Heb.	Hebrew	Tur.	Turkish
Hun.	Hungarian	Ukr.	Ukrainian
Ice.	Icelandic	Vie.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

A	angstrom(s)
ACTH	adrenocorticotropic hormone
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
BCG	Bacillus Calmette Guerin
bid	twice daily
C	degrees centigrade
cal	calorie(s)
kcal	kilocalorie(s)
cc	cubic centimeter(s)
Ci	curie(s)
mCi	millicurie(s)
μCi	microcurie(s)
cm	centimeter(s)
CNS	central nervous system
cpm	counts per minute
dl	deciliter(s)
ml	milliliter(s)
μl	microliter(s)
DNA	deoxyribonucleic acid
ED_{50}	median effective dose
EDTA	ethylenediamine tetraacetic acid
ESR	erythrocyte sedimentation rate
g	gram(s)
kg	kilogram(s)
mg	milligram(s)
μg	microgram(s)
Hb	hemoglobin
hr	hour(s)
ia	intra-arterial
ic	intracerebral
icav	intracavitary
id	intradermal
ILS	increased life span
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratumorous
IU	International Unit
iv	intravenous
K_m	Michaelis constant
LD	lethal dose
LD_{50}	median lethal dose
m	meter(s)
mm	millimeter(s)
M	molar
mM	millimolar
μM	micromolar
mOsm	milliosmolar
mEq	milliequivalents
min	minute(s)
mo	month(s)
MTD	maximum tolerated dose
N	normal concentration
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotidephosphate
NADPH	reduced nicotinamide adenine dinucleotide-phosphate
ng	nanogram(s) (10^{-9})
od	once daily
Pa	ambient pressure
PAS	periodic acid-Schiff
pg	picogram(s) (10^{-12})
pgEq	picogram equivalent
po	orally
ppb	parts per billion
ppm	parts per million
qid	four times daily
qod	every other day
QO_2	oxygen quotient
R	roentgen(s)
RBC	red blood cells (erythrocytes)
RNA	ribonucleic acid
sc	subcutaneous
sec	second(s)
SGOT	serum glutamic-oxalacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SRBS	sheep red blood cells
TCD	tissue culture dose
TCD_{50}	median tissue culture dose
tid	three times daily
U	unit(s)
mU	milliunit(s)
UV	ultraviolet
vol	volume
WBC	white blood cells (leukocytes)
wk	week(s)
wt	weight
x	times
yr	year(s)

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3601 PROBLEMS IN TRANSPLACENTAL CARCINOGENESIS. (Eng.) Zeller, W. J. (Institut fur Toxikologie und Chemotherapie am Deutschen Krebsforchungszentrum, Heidelberg, West Germany). *Indian J. Cancer* 12(1):21-29; 1975.

Data concerning diaplacental carcinogenesis with chemical carcinogens in animal experiments are reviewed, and a possible genetic mechanism for the transplacental production of nervous system tumors is discussed. Although most kinds of tumors found in adults are also observed in children and adolescents, the percentages of the various types of tumors differ in children and adults; thus, different mechanisms may be operative in adult and childhood cancers. Animal experiments with rats, mice, hamsters, and guinea pigs have shown that a considerable number of chemical substances can produce cancer diaplacentally in the descendents of mothers treated during pregnancy. Cancers occurring in advanced age may also be generated diaplacentally. Among 543 descendents of BD IX rats to whom a single dose of ehtylnitrosourea had been administered during gravidity, 821 malignant tumors of the nervous system were found. These experiments indicated that the fetal nervous tissue of rats is about 50 times more sensitive to ethylnitrosourea than the nervous tissue of adult animals. Even primarily noncarcinogenic substances were found to form carcinogens in the stomachs of the experimental animals; ethylurea and nitrite formed sufficient quantities of ethylnitrosourea in the stomachs of gravid mothers to produce cancer in all descendents. Other experimental results indicated that ethylnitrosourea can be absorbed through the skin of the pregnant rat in sufficient quantities to produce neurogenic tumors in the descendents. The fact that ethylnitrosourea did not produce neurogenic tumors in the offspring of mothers treated before the 12th day of pregnancy may have been due to increased hydrolysis of the carcinogen by the younger embryos. Additional experiments showed that the toxicity and carcinogenicity of ethylnitrosourea can be significantly increased by the addition of various heavy metals. Experiments are currently under way to determine if such an effect occurs transplacentally. (31 references)

3602 AFLATOXIN MUTAGENESIS. (Eng.) Ong, T. M. (Natl. Inst. of Environmental Health Sciences, P. O. Box 12233, Research Triangle Park, N.C. 27709). *Mutat. Res.* 32(1):35-53; 1975.

The chemistry, toxicity, carcinogenicity, teratogenicity, mutagenicity, and other genetically related activities of aflatoxins are reviewed. Twelve aflatoxin compounds are chemically recognized; these include aflatoxin B_1, B_2, G_1, G_2, B_{2a}, G_{2a}, M_1, M_2, R_0, Q_1, P_1, and GM_1. The toxic effect of aflatoxin has been demonstrated in many animal species; initial symptoms and relative toxicities are discussed. Aflatoxin carcinogenicity has been studied in various animals; both the lactone and the dihydrofurofuran portions of aflatoxin are necessary for the carcinogenic activities. Limited data on the teratogenic activity suggest a high degree of species specificity. Studies on the induction of chromosomal aberrations caused by aflatoxins have demonstrated abnormalities of chromosomal fragments, stickiness, bridges, chromatid breakage, and rearrangements. The most sensitive region is the heterochromatic area of the X chromosomes. The cytogenetic effects of aflatoxin in human WBC and in cells from rat kidney appear to be delay type, suggesting that aflatoxin is an alkylating agent. Studies on the induction of gene mutations have shown comparable relative frequencies of genotypes, allelic complementation, and nonpolarized complementation patterns induced by aflatoxin B_1 and G_1. Especially noteworthy is a quantitative relation of mutagenicity to interaction with DNA. While some studies on tumor induction have suggested that aflatoxin is active *per se*, others have indicated that metabolic activation is necessary. Tumor induction in only metabolically active cells, species-related teratogenicity, and definite organ specificity are cited. Other genetically related activities observed include induced phage production in lysogenic bacteria, inhibited DNA synthesis and inhibition of mitosis. The mutagenic hazard of aflatoxin is discussed in relation to aflatoxin distribution and contamination. A high cancer incidence has been found in certain geographic areas, and several studies have indicated that aflatoxin is responsible. Although direct evidence is still lacking, the induction of chromosomal aberrations in cultured human cells and the conversion of aflatoxin to mutagenic metabolites by human liver microsomes suggest a potential mutagenic hazard to man. (108 references)

3603 MORE ON THE AFLATOXIN-HEPATOMA STORY. (Eng.) Anonymous *Br. Med. J.* 2(5972): 647-648; 1975.

The role of aflatoxins and hepatitis B antigen in the etiology of primary hepatocellular carcinoma is reviewed. The geographical and cultural distribution of primary hepatoma in Africa suggests that a toxic environmental factor may be implicated in its pathogenesis. Surveys in Africa and Thailand, where primary hepatoma is common, have shown that up to 65% of groundnut (the staple diet of rural Africans) and 30% of the rice sampled may be contaminated with aflatoxin. Three separate surveys indicated that the greater the quantity of aflatoxin consumed, the greater the observed incidence of primary hepatoma. When data from these three studies were pooled, there was a definite correlation between the risk of developing primary hepatocellular carcinoma and the degree to which foodstuffs were contaminated with aflatoxin. Other studies have revealed a high frequency of hepatitis B antigen both in the general population and as a cause of cirrhosis in areas such as Africa, where hepatoma is common. It is possible that it is infection with hepatitis B antigen *in utero* or in early infancy that leads to hepatoma. In three Japanese families an association was uncovered between chronic presence of hepatitis B antigen acquired by transmission from mother to infant and primary hepatoma, usually associated with cirrhosis. A high proportion of hepatitis B antigen-positive patients with hepatoma have been found to have cirrhosis, leading to the suggestion that the neoplasm arises as a late manifestation of cirrhosis after hepatitis

due to hepatitis B antigen. It has also been suggested that hepatitis B antigen may act synergistically with aflatoxins to produce liver cancer. (28 references)

3604 MYCOTOXINS (Eng.) Austwick, P. K. C. (Nuffield Inst. Comparative Medicine, The Zoological Society of London, London, England). *Br. Med. Bull.* 31(3):222-229; 1975.

An assessment of mycotoxins as environmental chemicals is presented. The chemical nature and representative structure of the myctotoxins are noted; many are found to be well-known fungal metabolites. A discussion of the production of mycotoxins in the environment notes their origin from mostly pathogen or plant-decomposing fungi species, which in turn are dependent upon relative humidity, temperatures, general climate, the conditions of crop storage after harvest, and the geographical distribution of toxigenic strains of the fungi. The primary route of mycotoxin absorption is the consumption of an affected crop, while a secondary route is *via* consumption of the flesh or other products of an affected animal. Although the diagnosis of mycotoxicosis is dependent upon the elimination of other disease possibilities and the demonstration of the presence of an effective level of mycotoxin, the effects of mycotoxins in animals are well documented. Nonspecific symptoms of fungal hepatotoxicity are noted, and histopathological changes show distinct differences between the individual mycotoxins. Mycotoxin predilection for the kidney is also observed, rare direct neurotoxicity is noted, and few resultant outbreaks of skin lesions are found. Alimentary mycotoxicoses are characterized by ulceration and hemorrhage of the mucosa, the existence of pulmonary mycotoxicosis is suggested, and genitotoxins are demonstrated in pigs. Evidence of teratogenic change by fungal metabolites is accumulating, and especially cites cytochalasin B and aflatoxin B_1; there is also a positive correlation between aflatoxin consumption and high primary liver cancer rates. Furthermore, fungi are linked indirectly with toxicoses through their ability to induce plants to form systemic or local substances protective against invasion of the tissues. Rapid and accurate quantitative estimates of mycotoxin presence are available and their levels of control are suggested: (1) prevention of mycotoxin formation (2) prevention of mycotoxin consumption, and (3) prevention of action on the largest tissue *via* "protective feeding". (91 references)

3605 POLYUNSATURATED FATTY ACIDS AND COLON CANCER. (Eng.) Heyden, S. (Duke Medical Center, Duke Univ., Durham, N.C. 27710). *Nutr. Metab.* 17(6):321-328; 1974.

The possible co-carcinogenic effects of a highly polyunsaturated fatty acid diet are reviewed and disputed. An eight-year double-blind trial shows significantly more cancer deaths in the experimental group (31) than in the control group (17 cancer deaths), and implies a co-carcinogenic effect of the diet high in polyunsaturated fat. However, the revelation that only 19 of the 31 cancer victims in the experimental group had actually adhered to the prescribed diet negates that statistical difference, and is consistent with the hypothesis that the cholesterol-lowering diets do not influence cancer risk. Other studies also note no differences in the occurrence of colon-rectum cancer between controls and experimental persons, either in the dietary phase or post-diet phase. A retrospective study of 90 cases of colon cancer notes lower-than-expected initial levels of blood-cholesterol in the colon cancer patient; however, rather than being especially significant, the lowered cholesterol levels are viewed as obvious manifestations of a profound systemic derangement of the host metabolism. A literature review reveals no difference in dietary fat intake between colon cancer patients and controls, while an additional study finds no differences in the consumption of vegetables *vs* animal fat. The evidence presented thus exculpates polyunsaturated fatty acid diets from causing cancer, but still fails to interpret the cholesterol-colon cancer data. While there is abundant support of the hypothesis that the decreased intake of fiber and consequently decreased bowel-transit time is markedly associated with the high incidence of colonic cancer in the Western countries, the implication of polyunsaturated fatty acid diets is not supported by clinical experience, epidemiological research, or experimental studies. (9 references)

3606 DIETARY FAT IN RELATION TO TUMORIGENESIS. (Eng.) Carroll, K. K. (Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 3K7, Canada); Khor, H. T. *Prog. Biochem. Pharmacol.* 10:308-353; 1975.

The effects of dietary fat on tumorigenesis in animals, and epidemiologic data on dietary fat intake in relation to cancer mortality in humans are reviewed. Studies with experimental animals show an enhanced incidence of induced skin tumors in mice fed high fat diets; various sources of fats are utilized, and attempts to determine the effective fat components are noted. It is found that a high fat diet is generally more effective when fed after exposure to the carcinogen. Likewise, dietary fat also increases the incidence of spontaneous mammary tumors in DBA and C3H mice and in rats. While such enhancement is related to the amount of dietary fat, unsaturated fats have a greater effect than saturated fats. Similar results were found in studies on spontaneous mice hepatomas, aminoazo-dye-induced hepatomas, ^{131}I-induced hypophyseal tumors, and spontaneous intracranial tumors. Mouse tumors not enhanced by dietary fat include skin sarcomas and spontaneous and induced leukemia. A consideration of the possible mode of action of dietary fat suggests enhanced tumor incidence *via* facilitated carcinogen absorption, and/or augmented tumor induction *via* metabolic stimulation of potential tumor cells. Despite numerous complicating and contradictory factors, epidemiological data on humans indicate a selectively strong positive correlation between dietary fat intake and mortality from certain kinds of cancer, such as breast cancer, prostatic cancer, and cancer of the colon. However, other existing

data fail to show evidence of an association between cancer mortality and intake of unsaturated fat; factors of health care standards and other disease processes are also considered. It is further suggested that excess fat in the intestine may alter sterol and bile acid metabolism, possibly through changes in the bacterial flora. (140 references)

3607 HORMONES, GENES, AND CANCER. (Eng.) O'Malley, B. W. (Baylor Coll. Medicine, Houston, Texas). *Hosp. Pract.* 10(7):65-73; 1975.

The differentiation of the chick oviduct in response to estrogen was studied. A receptor protein, with the selective binding characteristics as the oviduct cells from which it was isolated, has a molecular wt of 227,000. It has two similar subunits and binds two molecules of estrogen/protein molecule. Ovalbumin mRNA increases within 30 min of estrogen stimulation of cells. A similar effect of progesterone was found. The study of hormone receptors may lead to a method for identification of hormone-dependent breast cancers. (No references)

3608 STILBESTROL-INDUCED ABNORMALITIES OF THE GENITAL TRACT IN YOUNG WOMEN. (Eng.) Herbst, A. L. (Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females, Warren 275, 275 Charles St., Boston, Mass. 02114); Scully, R. E.; Robboy, S. J.; Poskanzer, D. C.; Ulfelder, H. *Prog. Gynecol.* 6:647-668; 1975.

The epidemiological, clinical, and pathologic features of the vaginal and cervical cancers, based on an analysis of 170 cases entered in the Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females, is reviewed. In addition, the significance of the more frequent non-neoplastic abnormalities also related to prenatal exposure to synthetic hormones is also discussed. Use of stilbestrol, dienestrol, and/or other unidentified progestational medication has been noted in 78% of the cases. While carcinomas occur in girls exposed to a wide range (1.5-225 mg/day) of diethylstilbestrol (DES) doses, time of initiation is a significant factor. A peak occurrence is observed in the late teens; the present average age is 17.4 yr. Clinical features of abnormal vaginal bleeding or discharge, palpable tumors, and suspicious cytologic smears are frequently noted, while congenital urinary tract abnormalities are infrequently found. Histologically, the tumors have the same microscopic features as clear-cell adenocarcinomas occurring elsewhere in the genital tract, and are commonly associated with nonneoplastic alterations such as cervical erosion and vaginal adenosis. Following a brief review of the embryologic origin of the lower genital tracts, the histogenesis and pathogenesis of the DES-related abnormalities are discussed. Data indicate the early tumors adequately treated have an excellent prognosis, although some carcinomas have a virulent and fatal course. Various therapeutic approaches are used and advocated, depending upon the stage of the tumor and physician's preferences. These may involve: radical hysterectomy, vaginectomy, pelvic lymph node dissection, exenteration, local excision, and/or cancericidal radiation doses. The risk of carcinoma in the exposed population is evaluated, and screening of asymptomatic exposed girls by the age of 14 yrs is suggested. Screening examinations thus far reveal nonneoplastic vaginal abnormalities in 66%, and cervical abnormalities in 95% of DES-exposed subjects. Detection and management of vaginal adenosis and cervical erosion are discussed. It is established that prenatal exposure to DES and similar nonsteroidal estrogens results in frequent extensive cervical erosion and vaginal adenosis, but only rare development of clear-cell adenocarcinoma of the vagina and cervix. (41 references)

3609 RAUWOLFIA DERIVATIVES AND BREAST CANCER. (Eng.) O'Fallon, W. M. (Mayo Clinic, Rochester, Minn. 55901); Larbarthe, D. R. *Lancet* 2(7938):773; 1975.

An amendment to a previous report on the use of rauwolfia derivatives and the occurrence of breast cancer is presented. The rate of use of rauwolfia derivatives did not greatly change during the late 1960's and early 1970's. Of the whole cohort of hypertensive cases with breast cancer, 16.8% and 16.7% had been exposed to rauwolfia derivatives during the respective time periods. However, it is belatedly noted that while 29.4% of those diagnosed before 1971 had used other hypertensive agents, 35.3% of the whole cohort, i.e. until 1973, had such use. In contrasting hypertensive cases and controls diagnosed in the same time period, it was discovered that the breast cancer patients had not used thiazides, triamterene, or methyldopa more frequently than the controls. The general conclusion of the prior report, i.e., the lack of association between the use of reserpine and related drugs and breast cancer, is unaffected. (No references)

3610 AIR POLLUTION, SMOKING AND LUNG CANCER. (Eng.) Butler, J. D. (Univ. Aston, Birmingham B4 7ET, England). *Chem. Br.* 11(10):358-363; 1975.

The possible synergistic influences of cigarette smoking, air pollution, heavy metals, and carcinogenic polycyclic hydrocarbons on the development of lung cancer are discussed. In demonstrating the carcinogenic properties of many polynuclear hydrocarbons, a carcinogenic mechanism implicating hydroxylation of a methyl group is suggested. While atmospheric concentrations of benzo(a)pyrene are regarded as a measure of the total polynuclear hydrocarbons present, coronene concentration is considered a useful index of air pollution caused by motor traffic. The majority of such polynuclear hydrocarbons are found derived from the partial combustion of organic matter, *via* pyrolysis and subsequent rearrangement of the free radicals thus formed. Studies of the occurrence of polycyclic hydrocarbons note their proliferation in urban areas and their origination from heating oil and coal burning, refuse incineration, and combustion of propulsion fuel. British government records of atmospheric smoke and sulfur

dioxide levels indicate that, provided annual mean smoke concentrations are kept low, an average annual limit of 75-100 μg/M^3 of sulfur dioxide is acceptable. While only limited information on the distribution of polycyclic compounds near known sources is noted, seasonal fluctuations are found. A discussion of the isolation of such polycyclic hydrocarbons notes the required separation of particulate from adsorbate, followed by identification of individual compounds via alumina chromatographic columns, paper chromatography with fluorescence emission, spectrophotometry, or thin layer and gas chromatography. A survey of mortality and smoking habits reveals a linear relationship between average number of cigarettes smoked per day and the annual death rate, but notes a rapid reduction of the death rate following curtailment of cigarette smoking. While incompatible with the supposed 17 yr cancer development process, it suggests a co-carcinogenic effect of polycyclic hydrocarbons and other environmental factors. A multiple regression analysis correlating lung cancer mortality, cigarette smoking, solid fuel consumption, and benzo[a]pyrene concentrations is described. While acknowledging the possible synergistic influence of heavy metals, it is noted that the air pollution factor may be less significant, except for the premise that cigarette smoking is largely responsible for lung cancer. (24 references)

3611 THYROID IRRADIATION AND CARCINOGENESIS: REVIEW WITH ASSESSMENT OF CLINICAL IMPLICATIONS. (Eng.) Foster, R. S., Jr. (Univ. Vermont, Coll. Medicine, Burlington, Vt. 05401). *Am. J. Surg.* 130(5):608-611; 1975.

Data relative to carcinogenesis from thyroid irradiation are reviewed. Investigations of the clinical significance of the development of thyroid carcinoma have revealed a 75-80% incidence as a result of previous irradiation. Development of thyroid carcinoma after upper thoracic irradiation in infants is reported most commonly. Thyroid carcinoma is also related to irradiation for various benign conditions, and has a mean latent period of 20 yr. Both external irradiation and radioactive iodine increase the frequency of thyroid adenomas and thyroid carcinomas in rats. Goitrogen administration and partial thyroidectomy also increase the incidence of adenoma and carcinoma after irradiation. The dose-response relationship of irradiation induction of thyroid carcinoma is roughly bell-shaped; lower doses are less likely to induce malignancy. The risk of thyroid neoplasia increases linearly over the dose range of 20-1,125 rads to the thyroid. Accidental exposure to fallout containing radioactive iodine (150 rads) also results in a significant increase of benign and malignant thyroid neoplasms. Furthermore, a low incidence of neoplasia is anticipated due to the higher therapeutic dose (1,000-20,000 rads) of ^{131}I used for treatment of diffuse toxic goiter. However, surgical resection for nontoxic goiter has a much greater immediate risk than ^{131}I thyroid ablation in children, adolescents, and adults with Grave's disease. Whereas ^{131}I thyroid scans are noted capable of delivering a radiation dose of potential risk (50 μCi), use of technetium 99m is advocated. (36 references)

3612 THE CONCEPTS OF CRITICAL ORGAN AND RADIATION DOSE AS APPLIED TO PLUTONIUM. (Eng.) Stannard, J. N. (Univ. Rochester Sch. Medicine and Dentistry, Rochester, N. Y. 14642). *Health Phys.* 29(4):539-550; 1975.

The concepts of critical organ or tissue and calculation of radiation dose are discussed, and radiation and chemical hazard evaluation procedures are compared. The derivation of classical exposure standards for plutonium, with bone as the critical organ, are not based on calculation of a maximum permissible dose rate to that organ; rather, the plutonium body burden figure is related to the radium standard in man through comparison of the relative toxicity of plutonium and radium in animals. A comparison of maximum permissible body or organ burdens for plutonium-239 and polonium-210, based on several different criteria, shows that choice of criterion for a critical organ makes a large and significant difference in the resulting plutonium standards. Changes in models and modifications of metabolic parameters result in only slightly modified permissible plutonium levels. Consideration of the organ weight or volume and the possible significance of "hot particles" in such calculations is also discussed. On the basis of highest concentration and highest calculated doses, the respiratory lymph nodes are considered the critical organ for inhalation exposure to plutonium; however, it is further suggested that the lung and respiratory lymph nodes be taken together as a critical organ, with a combined weight of 1000 g. In the transfer from occupational to general population exposure standards, recommended maximum permissible annual dose rates attempt to employ a scaling factor and do not distinguish among organs. The lifetime and annual dose commitment concept is discussed, and the relationships between the procedures of risk estimation and the critical organ convention are examined briefly. It is noted that standards derived from plutonium risk estimates are in a different setting than those derived from the classical critical organ convention and from external radiation exposures. (43 references)

3613 LOW-LEVEL IONIZING RADIATION AND MAN. (Eng.) Diesendorf, M. (Dept. Applied Mathematics, SGS, Australian Natl. Univ., Canberra, Australian Capital Territory, Australia). *Search* 6(8):328-334; 1975.

Evidence that low doses of ionizing radiation may be harmful to man is reviewed. Medical and dental x-rays are the main source of man-made radiation exposure in Western countries. Selective exposure of individuals is a valuable tool of modern medicine, but in the case of unselective mass irradiations the risks may be greater than the benefits for the majority of people exposed. For most people exposed to compulsory mass chest x-rays in Australia, the estimated average risk of death from radiation induced cancer is greater than that from undetected

pulmonary TB. Realistic risk-benefit evaluations should take account of biologic variability. An equation for risk-benefit calculation is presented. (37 references)

3614 NUCLEIC ACID STUDIES ON THE PATHOGENESIS OF LEUKAEMIA. (Eng.) Polli, E. E. (Inst. Clinical Medicine I, Univ. Milan, Italy); Corneo, G. *Br. J. Haematol.* 31(Suppl.):155-164; 1975.

Review of recent work reveals strong support for the viral hypothesis of pathogenesis of human leukemia. In laboratory animals both horizontal and vertical transmission through subsequent generations occur. With some animal leukemias, and in general in human leukemia, virus-like particles have not been detected by electron microscopy. However, oncogenic virus infection can be transmitted through viral nucleic acids alone. Although the Epstein-Barr virus might be the agent of Burkitt's lymphoma, tumor viruses which cause leukemia in animals are usually RNA, and RNA viruses are more likely candidates as viral agents for human leukemia. RNA molecules with nucleotide sequences related to those of animal RNA tumor viruses have been found in human leukemia, lymphoma, sarcoma and carcinoma cells. Such RNA molecules have the size of 70S RNA and are associated with particles that form reverse transcriptase. Nucleotide sequences, related to sequences of known RNA tumor viruses, have been detected in human leukemic cell DNA. Viral DNA sequences appear to be mainly in the fraction having an intermediate repetition frequency. They are not enriched in the satellite DNAs, which are the most highly repeated sequence of the cellular genome. Normal cell genomes may contain endogenous viral sequences which are inactive and might have been transmitted vertically through many generations. Recent work with primates indicates that inherited RNA tumor virus sequences are related in related species of similar evolutionary origin. A primate RNA tumor virus, e.g. simian sarcoma virus, might be useful in the study of virus in human leukemia.

3615 SURFACE ANTIGENS ASSOCIATED WITH RNA TYPE C VIRUSES. (Eng.) Aoki, T. (Natl. Cancer Inst., NIH, Bethesda, Md.); Sibal, L. R. *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 243-247.

Type C virus envelope antigens (VEA) were investigated to determine their possible use in prophylaxis and immunotherapy and for an understanding of the oncogenesis of virus-induced tumors. VEA, glycoproteins with molecular wt of 69,000-71,000 daltons, are referred to as gp 69-71. In addition, gp 45, 60, and 70 were isolated from cell surfaces of murine leukemia virus (MuLV)-induced tumors. Antibodies to VEA show cytotoxic effects on the corresponding virus-producing and nonproducing malignant cells in the presence of complement. By demonstrating cell surface antigens (CSA) common to VEA with appropriate antiserum, unknown oncogenic RNA viruses may be detected in certain human tumors, although some mechanism may suppress the budding and/or maturation of the virus. Type C virus-induced CSA, other than those associated with MuLV, are the sarcoma virus-induced CSA. Although murine sarcoma virus (MSV) obtains its viral envelope from MuLV and/or endogenous type C viruses, immunoelectron microscopy demonstrated that *in vitro* MSV-transformed and subcloned mouse- and rat-nonproducer cells induce a small amount of common specific CSA different from the MuLV and its induced antigens. MSV requires type C viral envelope from helper viruses to replicate *in vitro* and *in vivo*. Natural antibodies, IgG and IgM classes, to CSA and VEA were of type C virus-induced tumors and occur naturally in a variety of inbred strains and F_1 hybrids of mice. Natural antibodies to these antigens were found in the kidney antigen-antibody complexes in mouse strains with high incidences of spontaneous leukemia. Consequently, the presence of natural antibodies to VEA in free form suggests that these antibodies play a role in the suppressive mechanisms of type C virus maturation and oncogenesis in resistant mice strains. Since, these antibodies have been detected in several species other than the mouse, it seems possible that an antibody occurring in humans suppresses the maturation of possible human type C viruses. By passive immunization with antiserum to VEA, both prophylaxis and treatment of virus-induced tumors may be achieved. (32 references)

3616 VACCINATION AGAINST HERPES GROUP VIRUSES. (Eng.) Plotkin, S. A. (Children's Hosp. Philadelphia, 34 Civic Center Blvd., Philadelphia, Pa. 19104). *Pediatrics* 56(4):494-496; 1975.

Problems involved in the development of herpes virus group vaccines are summarized. A major factor is the possible oncogenicity of human herpes viruses. Several herpes viruses of animals have been shown to be oncogenic in homologous or heterologous species. Although irradiated human cytomegalovirus (CMV) was reported to transform hamster embryo fibroblasts, no epidemiologic evidence yet implicates either human CMV or varicella-zoster (V-Z) in the causation of malignancy. Whereas almost all herpes viruses have the capacity to maintain the viral genome in a noninfectious state and subsequently reactivate, the persistence of herpes viruses in latent form is a second major concern. However, if their replication is localized, attenuated vaccines may not result in enough virus to cause widespread infection. A balancing of the possible ill effects of attenuated CMV or V-Z viruses against the actual effects of the wild viruses is suggested. The importance of cellular immunity in protection against herpes viruses is also discussed. Live vaccines are expected to induce cellular and humoral immunity equal to that derived from infection. Effective veterinary vaccines thus developed include attenuated Marek's disease vaccine, killed *Herpes virus saimiri* vaccine, and partly attenuated mouse CMV vaccine. Arguments for cautious optimism in the development of herpes virus vaccines note the resultant brain damage of CMV infected infants, the mortality associated

with complications of varicella, and the enormous morbidity of zoster. (29 references)

3617 IDIOTYPE-POSITIVE T LYMPHOCYTES. (Eng.) Binz, H. (Uppsala Univ. Medical Sch., Box 562, 751 22 Uppsala, Sweden); Kimura, A.; Wigzell, H. *Scand. J. Immunol.* 4(5/6):413-420; 1975.

Studies suggesting that B and T lymphocytes may use identical genetic material for the buildup of their respective antigen-binding sites on the receptor molecules are reviewed. Several sets of observations have indicated that B and T lymphocytes reactive against the same antigenic determinants express shared idiotypic determinants on their respective antigen-binding receptors. Two systems especially discussed are in the rat and the mouse, using the major histocompatibility Ag-B and the group A streptococcal carbohydrate antigenic determinants as the immunogen, respectively. Data indicate that the antigen-binding receptors used by T and B lymphocytes use similar if not identical genetic material in the construction of their respective antigen-binding areas. The favored interpretation is that of shared idiotypes. Anti-idiotypic antibodies have been used to directly visualize and enumerate idiotype-positive lymphocytes, *via* fluorescent antibody techniques, autoradiography, or cytofluorimetry. The idiotypic-positive T lymphocytes have thus been shown to constitute a clearly distinct group of cells. In addition, separation data from affinity chromatography have demonstrated the existence of physically separable normal T lymphocytes with largely non-overlapping immune reactivity against Ag-B antigens. Preliminary findings suggest that while the B-cell product is a two-strand chain structure, the released T-cell receptor behaves like a single chain under reducing-alkylating conditions. The released receptor molecule has a size of around 35,000 daltons, and probably involves additional genetic material to that of the heavy-chain V genes. (41 references)

3618 THE RELATIONSHIP BETWEEN CUTANEOUS AND VISCERAL CARCINOMAS [editorial]. (Eng.) Maize, J. C. (State Univ. New York at Buffalo, Sch. Medicine, Buffalo, N. Y.). *J.A.M.A.* 233(9): 986; 1975.

The relationship between cutaneous carcinoma and visceral malignant neoplasms has long been a subject of controversy. Researchers at the Finsen Institute in Denmark have recently found no appreciable deviation from the expected incidence of visceral neoplasms in patients with either Bowen disease or multiple basal cell carcinomas. Their conclusion in the case of Bowen disease differs considerably from that of U.S. authors. In more than one quarter of 155 patients with Bowen disease, a primary extracutaneous malignant neoplasm developed an average of five to six years after onset of the cutaneous tumor. Treatment of the Bowen disease had no effect on the subsequent development of systemic malignant neoplasm. An incidence of internal carcinoma of 15% to 22.6% in patients with Bowen disease has been reported by others. The yield of internal neoplasms generated by a thorough evaluation of patients with basal cell or squamous cell carcinomas of the skin is not appreciably higher than in the uninvolved population of similar age. It would seem advisable to assess and observe patients with Bowen disease carefully, for the development of internal neoplasms.

3619 IMMUNITY IN CANCER. (Eng.) Seibert, F. B. (Res. Lab., Veterans Administration Center, Bay Pines, Fla. 33504). *Science* 190(4216): 809; 1975.

The reduction in the occurrence of mammary tumors in C3H/He mice given injections of poly(A)•poly(U), living LDH-virus, or heat-killed C3H ♀ 27 Brtu bacterium vaccine is briefly reviewed. In all three sets of experiments, a 20% increment of survival was effected. A subsequent 90-100% tumor incidence in treated mice, after 380 days, suggested a loss of cellular immunity and/or delay of spontaneous tumor development. The advantages of a sterile autogenous or homologous vaccine are noted, and the problem of live or dead bacterial contamination is acknowledged. (5 references)

3620 ULTRASTRUCTURE OF MAMMALIAN CHROMOSOME ABERRATIONS. (Eng.) Brinkley, B. R. (Univ. Texas Medical Branch, Galveston, Tex.); Hittelman, W. N. *Int. Rev. Cytol.* 42:49-101; 1975.

The spectrum of chromosome damage produced by various natural and synthetic clastogens as evaluated by both light and electron microscopy is described. Various aspects of detectable chromosome damage are compared. These include: chromosome-type aberrations, chromatid-type aberrations, gaps, exchanges, subchromatid aberrations, chromosome stickiness, and damage to specialized chromosome regions. Ultrastructural studies generally confirm light microscope analyses. There is some controversy between the two techniques, over aberrations scored as breaks *vs* gaps. In chromatid breaks viewed by the electron microscope, the broken region is characterized by an absence of interconnecting fibrils between the two broken parts. Ultrastructural studies suggest that such breaks may be either aligned or unaligned. Chromatid gaps appear composed of several size classes of chromatin fibrils, as indicated by ultrastructural analysis on isolated chromosomes and ultrathin sections. Exchanges effected by chromatid breaks, and subchromatid aberrations such as side-arm bridges, are also more clearly defined by electron optics. In both side-arm bridges and chromosome stickiness, thin "subchromatid" fibrils are observed between daughter chromatids at metaphase, anaphase, and telophase. While somewhat ineffective as a tool for evaluating metaphase chromosome strandedness in eukaryotic cells, transmission electron microscopy reveals damage to specialized regions such as the kinetochore, and nucleolar organizer. Analysis of the chromosome target of ionizing radiations,

alkylating agents, and metabolic agents implies a correlation between DNA breakage and the induction of chromosome aberrations. Such agents may induce immediate aberrations or unbalanced growth; aberrations reflect the state of the chromatin at the time of treatment. Several models for the formation of the initial chromosome lesion are presented, all of which involve breakage of chromatin fibers. (143 references)

3621 TERATOCARCINOMA CELLS CAN DEVELOP NORMALLY. (Eng.) Hogan, B. (No affiliation given). *Nature* 258(5530):12-13; 1975.

Several experiments illustrating that teratocarcinoma cells can participate in normal morphogenesis and differentiation are reviewed. An initial study of teratocarcinomas employs the 129/Sv strain of mice, observed to have a high frequency of spontaneous testicular teratocarcinoma of germ cell origin. The tumors are found transplantable in either a solid or ascites form, the latter of which exhibits an arrangement similar to the organization of very early mouse embryos. Later studies established that transplantable teratocarcinomas can also be obtained from many different strains of mice by injecting (male or female) embryos of up to seven days development into extrauterine sites. *In vitro* attached and suspension cultures of embryo bodies proliferate to form a multi-layered, differentiated tissue sheet; clonal populations of homogenous cells are also observed. Injection of embryonal carcinoma cells from simple embryoid bodies from ascites fluid into four day mouse blastocysts of a different genotype results in one chimaeric animal. Injection of 121 animals born from blastocysts innoculated with cultured teratocarcinoma cells, 11 display chimaerism, a proportion of which developed tumors. The overall results suggest that at least some cultured teratocarcinoma cells are able to participate in normal development, and implies that mutants of the cultured cells can be utilized in studies of metabolic cooperation and cell interaction during development. (6 references)

3622 PRELIMINARY AND EARLY STAGES OF BREAST CANCER. (Ger.) Altenahr, E. (Pathologisches Institut der Universitat, 2 Hamburg 20, Martinistr. 52 West Germany); Kracht, J. *Dtsch. Med. Wochenschr.* 100(40):2053-2054; 1975.

Etiological, histological, staging, and therapeutic aspects of carcinoma of the female breast, as discussed in the section Gynecological Pathology of the German Society of Pathology at its 59th Conference, are presented. The observed low incidence of breast cancer among women who are primiparous at the age of 18-19 yr is tentatively explained with the considerable reduction of the concentration of cell-bound environmental carcinogens accumulated during puberty. This reduction is explained as being due to active mitosis of the gland cells and to apocrine secretion after parturition at a young age, i.e., before these carcinogens could provoke any cell transformation. The increased incidence of breast cancer among women who are primiparous at a more advanced age is consequently due to an epithelial cell transformation by the strongly accumulated carcinogens at an age when the dilution effect resulting from cell division can no longer stem the cell transformation and dedifferentiation.

3623 PREDISPOSING FACTORS IN CARCINOMA OF THE COLON. (Eng.) Sherlock, P. (Mem. Sloan-Kettering Cancer Cent., New York, N.Y.); Lipkin, M.; Winawer, S. J. *Adv. Int. Med.* 20:121-150; 1975.

The predisposing factors in carcinoma of the colon including environmental, genetic, immunologic, and cellular aspects are reviewed and the management of premalignant clinical conditions is discussed. Colorectal carcinoma is a disease of "advancing civilization," accounting for 15% of all malignant neoplasms and the second cause of death from cancer in the U. S. Geographically, the incidence of colonic cancer is high in north and west Europe, New Zealand, and North America and low in South America, Africa, and Asia. Epidemiologic investigations suggest that diet and bacteria produce metabolic products that can act as carcinogens or co-carcinogens within the lumen of the colon; i.e., feces from populations with a high colonic cancer incidence contain significantly more *Bacteroides* and *Clostridium* species and fewer streptococci and lactobacilli. High incidence of colonic cancer is found in individuals consuming diets rich in fat and animal protein and in whom fecal matter contains a high concentration of neutral and acid sterols and bile acid derivatives. Experiments with animal models suggest that specific changes occur during neoplastic transformation of colonic cells of man. These changes develop in areas of cell metabolism that increase DNA synthesis within the cells and enhance the cells' ability to proliferate. In addition, immunologic investigations have led to the development of procedures involving the detection of tumor antigens. Although cancer of the colon and rectum are largely influenced by environmental factors, the genetic susceptibility is considered and may be helpful in assessing mucosa at risk. Several genetic syndromes with a predisposition to malignant change are transmitted by a single gene; however, there are some familial aggregations of colonic cancer that do not fit the predicted mendelian ratio. Thus far, carcinoma of the colon appears to have a genetic basis that resists analytic efforts to prove a single-gene difference, except for the familial polyposis syndrome. Continued exposure to carcinogenic influences (as in chronic inflammations) may be responsible for the development of malignancy in ulcerative colitis; definite criteria have been established for assessing the potential malignancy of the disease. A controversy continues to surround the premalignant character of adenomatous polyps; arguments for and against adenomatous polyps as precursors of cancer of the colon and rectum are presented. Although sigmoidoscopy, biopsy, and barium enema with air contrast remain important diagnostic techniques, fiberoptic colonoscopy better defines suspicious areas and permits the removal of many of the lesions without major surgery. The authors conclude that

a technique employing biochemical or immunologic measurements to indicate malignancy potential of colonic lesions would be most useful for the prevention and management of cases of colonic cancer. (96 references)

3624 NON-MYOGENIC TUMORS INVOLVING SKELETAL MUSCLE: A SURVEY WITH SPECIAL REFERENCE TO ALVEOLAR SOFT PART SARCOMA. (Eng.) Delaney, W. E. (St. Vincent's Hosp. and Medical Center of New York, New York, N. Y. 10011). *Ann. Clin. Lab. Sci.* 5(4):236-241; 1975.

The distinctive non-myogenic tumor which occurs exclusively in skeletal muscle, alveolar soft part sarcoma, is the subject of this review. This tumor has ultrastructural features of a secretory lesion with distinctive membrane-bound crystalloids which may be lipid in nature. The ultrastructural features of alveolar soft part sarcoma do not support a myogenous derivation. This clinically indolent, malignant tumor, occurring exclusively in skeletal muscle, probably originates in the paraganglia. (14 references)

3625 MORPHOLOGY AND CLASSIFICATION OF MALIGNANT LYMPHOMAS AND SO-CALLED RETICULOSES. (Eng.) Lennert, K. (Dept. Pathology, Univ. Kiel, Postfach 4324, D-2300 Kiel, Germany). *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:1-16; 1975.

An introductory survey of the classification and morphology of Hodgkin and nonHodgkin malignant lymphomas and reticuloses is presented. Such a reclassification involves the application of immunochemical, immunomorphological, histological, histochemical, cytological, and ultrastructural techniques. Hodgkin's disease is classified into four categories: (1) lymphocytic predominance, (2) nodular sclerosing, (3) mixed, and (4) lymphocytic depletion. Three types of reticuloses originally distinguished as small, medium-sized, and large cell variants are now interpreted as hairy cell leukemia, myeloid leukemia, and variant of immunoblastic sarcoma, respectively. A simple scheme demonstrating the basic cytological correlations of thymus-derived (T-) and bone marrow-derived (B-) lymphocytes is discussed in detail. Several classifications of malignant lymphomas are compared, and the essential points of the Kiel classification are noted. This classification distinguishes two main groups of malignant lymphomas, omits the use of the words "lymphosarcoma" and "leukemia", considers the so-called reticulosarcomas as malignant lymphoma, immunoblastic, and substitutes the terms centroblast and centrocyte for germinoblast and germinocyte, respectively. The low-grade malignant lymphomas, suffixed "-cytic", include lymphocytic lymphomas of the subtypes chronic lymphoid leukemia, hairy cell leukemia, and mycosis fungoides, lymphoplasmacytoid or immunocytic lymphoma, centrocytic lymphoma, and centroblastic/centrocytic lymphoma. The high-grade malignancies, suffixed "-blastic", include centroblastic malignant lymphoma, lymphoblastic lymphoma, including Burkitt and convoluted cell types, and immunoblastic lymphoma. In addition, true reticulosarcoma is noted to exist. A correlation of the different non-Hodgkin lymphomas with the cytological scheme reveals that the T-cell series includes lymphoblastic lymphoma of the convoluted type and Sezary syndrome, while most non-Hodgkin lymphomas are of B-cell origin. (49 references)

3626 THE ROLE OF THE SPLEEN IN TUMORS AND LEUKEMIAS (LITERATURE REVIEW). (Rus.) Zverkova, A. S. (Kiev Scientific Res. Inst. Hematology and Blood Transfusion, Kiev, USSR). *Vrach. Delo* (7):80-83; 1975.

Observations on the role of the spleen in malignant processes are reviewed. A very low incidence of primary tumors and metastases is characteristic for the spleen as compared with other inner organs. Splenectomy was found to lead to the loss of immunity to tumors in certain tumor-resistant animal species, and splenectomy in humans and animals was found to accelerate and aggravate the development and course of malignant tumors and leukemia, and to provoke the transformation of one tumor type in another, more malignant one, e.g., of chronic reticulosis into reticulosarcomatosis. The transplantability of certain leukemia cell lines was found to increase considerably following splenectomy in animals. The implantation iv or ip injection of normal or immunized spleen cells or cell extracts has been demonstrated to inhibit the tumor growth and to prolong the survival in humans and animals. The literature data indicate the important immunological and antineoplastic role of the spleen, and the impairment of certain immunological and antitumor functions of the spleen in leukemia (reduced antibody formation and phagocytic activity of the spleen). The mechanism of the antineoplastic action of the normal spleen may be due to the living cell or to a chemical agent. (52 references)

3627 RECENT PERSPECTIVES IN OCCUPATIONAL CANCER. (Eng.) Selikoff, I. J. (Mount Sinai Sch. Medicine, Fifth Ave. and 100 St., New York, N.Y. 10029). *Ambio* 4(1):14-17; 1975.

Recent developments in the study of occupational cancer are reviewed, including the identification of previously unsuspected carcinogenic agents and the evaluation of materials used in industry and/or agriculture. A considerable amount of time (usually 20-35 yr) must elapse between exposure to an occupational carcinogen and the onset of disease. Therefore, epidemiologists must depend on other disciplines to identify carcinogenic substances that have been introduced within the last 50 yr. Other investigations indicate the possibility of the interaction of two or more agents. Asbestos workers with a history of cigarette smoking had 92 times the risk of death from lung cancer compared with individuals of the same age who neither worked with asbestos or smoked. Substances that may have no carcinogenic effect by themselves may, in concert with others, have an additive or multiplicative effect on malignancy and other substances, deemed innocuous in one environment, may be carcinogenic in a new environment. Two neoplasms, hemangiosarcoma of the

liver and mesothelioma, infrequent in general but common with industrial exposure demonstrate the importance of "signal" tumors in the identification of occupational carcinogens. The principles of carcinogenic risk derived from occupational sources is important for the control of environmental cancer, whether it is from radiation-producing power sources, agricultural use of pesticides, air and water pollution from petrochemical industry, carcinogenic mineral dust, or other substances or processes. Generally, malignancy increases with intensity and duration of exposure to the carcinogen and theoretical considerations indicate that there is no identifiable lower threshold limit for carcinogenic agents. Recognition of the long period of clinical latency between occupational exposure to carcinogens and their effects indicates the need for procedures to screen possible carcinogenic agents. Priorities for the selection of agents to be tested should include chemical structure, other biological activity, and number of workers likely to be exposed. (34 references)

3628 BONE CANCER: EPIDEMIOLOGIC AND ETIOLOGIC CONSIDERATIONS. (Eng.) Fraumeni, J. F., Jr. (Natl. Cancer Inst., Bethesda, Md. 20014). *Front. Radiat. Ther. Oncol.* 10:17-27; 1975.

Epidemiological observations and peculiarities of bone cancer are reviewed, and etiologic suggestions are discussed. Occurrence patterns reveal a bimodal age curve in U.S. mortality from bone cancer, with peaks at 15-19 yr and after 65 yr; the rates are generally greater in whites than nonwhites, and in males than females. However, particularly high rates for bone cancer in older adults are reported in England, while no such increases are found among the elderly in Japan. A three-year survey of 10% of the U.S. population reports 515 cases of primary bone cancer, mainly osteogenic sarcoma, chondrosarcoma, and Ewing's tumor. An analysis of childhood bone cancer deaths notes a rapid increase of death from osteogenic sarcoma in late childhood in both sexes; Ewing's sarcoma also shows a progressive increase with age and diverging mortality between the sexes in adolescence, plus a significant absence among nonwhites. While ionizing radiation is the only environmental agent known to produce bone cancers, tumors are also linked to high dose (therapeutic) irradiation and internal bone-seeking radioisotopes. Several laboratory observations, including that of virus-induced osteosarcomas in mice and chickens, suggest a role of infectious agents in bone cancer; seasonal variation and possible vertically-transmitted viruses are also noted. While no chemically-induced bone tumors are identified in man, osteosarcoma is produced in rabbits by iv administration of certain beryllium compounds. A discussion of host factors noted that certain syndromes of skeletal maldevelopment are prone to bone cancer, yet cannot suggest that immunodepression or chromosomal defects generally predispose to bone cancer. Several familial aggregates of bone cancer are described, and the occurrence of multiple primary bone neoplasms and multicentric involvement without precursor lesions suggests especial susceptibility. The dramatically increased rates for osteogenic sarcoma during adolescence are correlated with skeletal growth patterns, pubertal growth patterns, and skeletal stress. Whereas the role of genetic susceptibility and familial susceptibility mechanisms is suggested, regular follow up of persons with these and other predisposing conditions is advised. (49 references)

3629 CUTTING OUT CANCERS. (Eng.) Swaffield, L. (No affiliation given). *Nature* 258(5531):94-95; 1975.

The international standards of protection of workers against carcinogens, as constructed at the International Labour Conference (ILC), are reviewed and evaluated. Major inadequacies arise from the preoccupation with finding a dramatic breakthrough cure, the great latitude allowed individual nations, and the economic realities. Two case histories illustrate the extremes of negligent and diligent industrial concern: production of an anti-oxidant containing 2-naphthylamine (Nonox S), and vinyl chloride monomer production, respectively. Whereas attempts to trace and control all carcinogens appear economically unfeasible, the individual nations are to decide the acceptable social and economic risk. The ILO convention requires replacement or control of carcinogens and a system of records kept. Further recommendations include the promotion of epidemiological studies and production of educational guides. However, international cooperation on occupational health research is acknowledged to be very poor. (no references)

3630 INCIDENCE OF NEOPLASIAS OF THE BLADDER IN THE TWO SEXES. (A SURVEY CONDUCTED AMONG UROLOGISTS IN SPAIN). (Spa.) Cifuentes Delatte, L. (No affiliation given). *An. R. Acad. Nacl. Med. (Madr.)* 92(3):483-499; 1975.

A review of 17,416 cases of bladder neoplasms in Spaniards between 1950-1974, revealed a male:female incidence ratio of 7.24:1. Ranging from a high of 14.1:1 in the Canary Islands to a low of 5.25:1 in the Basque Provinces. This ratio is higher than other comparative studies published in England, Japan, Sweden and the U.S.A. These results ranged between (2.51:1 to 4.74:1). The high incidence of bladder neoplasms in Spanish males is attributed to: 1) increased use of tobacco among men, and 2) greater exposure to industrial toxins. i.e. aniline and alpha- and beta-naphthylamine. Other compounds associated with bladder neoplasms were: food dyes, coffee contaminated with 3,4-benzpyrene, phenacetin, cyclamates, and schistosomiasis. A panel discussion of Spanish urologists urged: 1) greater study of industrial compounds (e.g. plastics) as possible carcinogens. 2) a campaign against the use of tobacco. (no references)

3631 *IN SITU* CYTOLOGIC NUCLEIC ACID HYBRIDIZATION AND ITS RELATION TO CANCER. (Eng.) McDougall, J. K. (Medical Sch., Univ. Birmingham, Birmingham B15 2TJ, England). *Proc. Int. Cancer Congr. 11th.* Vol. 1 *(Cell Biology and Tumor Immun-*

ology). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 100-102.

The use of molecular hybridization methods and autoradiographic detection in the study of satellite and viral DNA sequences is described. The techniques employ purified nucleic acids from cells or viruses in the examination of sequence complexity by renaturation in solution or detection of complementary sequences immobilized on membranes. Satellite DNA sequences are localized on the chromosomes of many species, ribosomal cistrons are mapped in man, and globin messenger RNA is also localized by *in situ* hybridization with *in vitro* transcribed complementary DNA. Despite the confusion of polymorphisms, the persistence of unique sequences in tumor cells representing viral genes has been demonstrated. *In situ* hybridization studies have detected virus DNA in virus-transformed and tumor cells, and in situations where the virus may exist in a latent infection state. Membrane hybridization has revealed Epstein-Barr virus DNA in nasopharyngeal carcinoma, while *in situ* hybridization has shown that the viral genomes are present in the epithelial cells of the tumor. An association of Epstein-Barr virus genomes with host cell chromosomes has also been indicated. The *in situ* method showed the presence of herpesvirus DNA in four specimens from 11 biopsies of cervical carcinoma specimens. The hybridization of adenovirus cRNA to virus-infected or transformed rodent interphase and metaphase cells also indicates a random association of viral DNA with the chromosomes. Thus it is noted that *in situ* hybridization studies can demonstrate the localization of viral genes in tumor cells. (30 references)

3632 LIPOPROTEINS IN RELATION TO CANCER. (Eng.) Barclay, M. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021); Skipski, V. P. *Prog. Biochem. Pharmacol.* 10:76-111; 1975.

The measurement, quantitation, and patterns of serum lipoprotein levels in normal humans and cancer patients is reviewed. While there is presently no evidence that the lipoprotein fractions from various groups of normal fasting subjects have remarkably different amounts or kinds of lipids or proteins, lipoprotein levels are influenced by a variety of factors in health and disease. Therefore, the careful selection and description of "normal" subjects and cancer patients is discussed. Normal (fasting) women have values for total very low-density lipoproteins (VLDL) of 7-12 mg/100 ml serum, with very low standard deviations. However, normal men with a positive family history of cancer have elevated values for total VLDL (73-296 mg/100 ml serum) and more variability ($\pm$ 91); likewise, all cancer patients report significantly higher levels of total VLDL, resulting primarily from the components with S_f20-100 and S_f0-20. Of the three classes of low-density lipoproteins (LDL) recognized, ultracentrifugal techniques show low and similar values (0.84 mg/100 ml serum) for the S_f10-20 class in normal subjects, very high and variable S_f10-20 values (0-433 mg/100 ml serum) in women with breast cancer, and high S_f0-3 values (15-27 mg/100 ml serum) in men with various cancers. Such LDLs are seen less sensitive to the diet than VLDLs, and rarely elevated in children with various kinds of cancer. Use of ultracentrifugation, electrophoretic, and precipitation techniques show lower average levels of high-density lipoproteins (HDL_2 and HDL_3) in both normal women and men with pronounced family histories of cancer (26-86 mg/100 ml serum and 16-46 mg/100 ml serum, resp.). While normal HDL_2 values range from 93-186 and 70-122 mg/100 ml serum resp., unusually low HDL_2 values of 15-54 mg/100 ml serum are found in men with various cancers. Lowered α-lipoprotein (HDL) values are also reported with the growth of pregnancy, but are assumed to be related to cancerous growth. Patients with gynecological malignancies also have higher average serum concentrations of free fatty acids than normal subjects, i.e. 20.4 *vs* 13.6 mg/100 ml serum, with especially notable decreases in linoleic acid and increases in stearic and palmitic acid levels. Studies on animals with experimental tumors report similar observations, but qualitative and quantitative differences in VLDL, LDL, HDL_2 and HDL_3 levels than observed in human subjects. It is noted that VLDL elevates concurrently with significant decreases in HDL_2 and that unusually high HDL_1 values concur with significantly lowered values for other HDLs. The patterns occur especially and strikingly in male cancer patients, but are also observed in women with cancer. (66 references)

3633 ISOENZYMES IN CANCER. (Rus.) Komov, V. P. (Inst. Chem. Pharmaceut., Leningrad, USSR). *Vopr. Onkol.* 21(4):80-87; 1975.

Studies on changes of different isoenzyme spectra in connection with benign and malignant tumors in the human or animal organism are reviewed. Malignant transformation was found to be accompanied by an increase in the level of muscular and hepatic forms of lactate dehydrogenase (LDH) isoenzymes. Reduction of the H-form of LDH in leukocytes was observed in human leukemias. Considerable changes were found in the isoenzyme spectra and catalytic functions of aldolase, hexokinase, catalase, alkaline phosphatase, DNA-polymerase, uridine cytidyl kinase, serine transoxymethylase, desoxymethydyl kinase, pyruvate kinase, and other enzymes in the presence of malignant process. The presence of hexokinase in the serum of cancer patients is believed to be due to the increased permeability of the cell membrane. The decreased catalase activity in the liver of tumor-bearing animals was found to return to normal after tumor extirpation. One of the four catalase isoenzymes was fully inhibited in patients with lung cancer, but qualitative normalization of the isoenzyme spectrum was observed 22 days after radical surgery. Two catalase isoenzymes were inhibited in patients with gastric carcinoma. The studies indicate the inhibition of one or more isoenzymes or the appearance of additional isoenzymes without any qualitative change in the isoenzyme spectra in the presence of malignant process. The different changes in the isoenzyme spectra are very likely to be dependent of the nature of the enzyme, the mode of the synthesis of the isoenzymes, of the tissue specificity, and sometimes even of the localization of the tumor. Changes in the quantitative

relationships and in the intracellular localization of the isoenzymes, resulting in distinct departure from the normal biochemical processes and in the metabolism in the malignant tissue, are hypothesized to occur in tumor cells. (72 references)

3634 CYTOPLASMIC CONTROL OF NUCLEAR ACTIVITY. (Eng.) Birnie, G. D. (Beatson Inst. Cancer Res., 132, Hill St., Glasgow, G3 6UD, Scotland). *Proc. Int. Cancer Congr. 11th.* Vol. 1 *(Cell Biology and Tumor Immunology).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 84-88.

In vivo and *in vitro* studies on cytoplasmic control of DNA synthesis, RNA synthesis, and gene expression are reviewed. *In vivo* experiments using cell fusion and nuclear transplantation techniques have demonstrated a bidirectional flow of information between the nucleus and cytoplasm. The effect of environmental changes on nuclei has been demonstrated using nuclei of hen erythrocytes. Autoradiographic studies have demonstrated that reactivated hen erythrocyte nuclei synthesize RNA, while studies on hen erythrocyte-rabbit macrophage heterokaryons have indicated that the active partner is the dominant one, that stimulatory factors are located in the cytoplasm, and that activation is not due to direct transference of factors. Studies using HeLa cell lysates and soluble extracts of cultured mouse kidney cells have shown that the low level of DNA synthesis is stimulated by the addition of a soluble cytoplasmic extract from the same cell; however, very little stimulation occurred when the nuclei were incubated with a similar cytoplasmic extract prepared from mycoplasma-infected cells. In contrast, while nuclei from infected cells synthesize DNA at a higher rate, cytoplasmic extracts from uninfected cells do not significantly stimulate that rate. Although prone to artifacts resulting from nuclease and protease activities, the use of cell-free systems has shown that addition of cytoplasmic extracts from growing cells results in a brief but pronounced stimulation of the rate of RNA synthesis. Experiments on isolated chromatin have shown that mouse-brain chromatin reassociated in the presence of nonhistone proteins from mouse fetal liver results in a nucleoprotein complex from which globin-specifying messenger RNA sequences can be transcribed. The activation of a dormant nucleus may be at least partially due to the absorption of specific nonhistone proteins from the active cytoplasm. There is also evidence that the phosphorylation of chromatin nonhistone proteins is linked with the control of gene activity, as suggested by the observation that cytoplasmic proteins stimulate the release of pre-existing RNA from isolated nuclei. Qualitative and quantitative differences between the populations of polyadenylated RNA molecules in nuclei and cytoplasm are indicated. Results suggest that soluble cytoplasmic factors may affect the post-transcriptional control of the regulation of gene expression in eucaryotes. (21 references)

3635 EXPERIMENTAL GASTRIC CANCER IN THE DOG AND OTHER EXPERIMENTAL ANIMALS. A SURVEY OF THE PRESENT STATUS. (Eng.) Nagayo, T. (Aichi Cancer Center, Res. Inst., Nagoya, Japan). *Proc. Int. Cancer Congr. 11th.* Vol. 6 *(Tumors of Specific Sites).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 215-219. (16 references)

3636 HEPATOMA ASSOCIATED WITH ANDROGENIC STEROIDS. (Eng.) Anthony, P. P. (Middlesex Hosp., London W1N 8AA, England). *Lancet* 1(7908):685-686; 1975. (12 references)

3637 STEROIDAL CONTRACEPTIVE THERAPY: HEPATOMAS AND VITAMIN A. (Eng.) Gal, I. (Dept. Biological Sciences, Hatfield Polytechnic, Hatfield, Herts, England). *Lancet* 1(7908):684; 1975. (14 references)

3638 PROLACTIN AND BREAST CANCER. (Fre.) Cappelaere, P. (Institut de Recherches sur le Cancer de Lille, Boite Postale 3569, 59020 Lille Cedex, France). *Pathol. Biol. (Paris)* 23(2): 161-170; 1975. (79 references)

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3641 RADIOLOGICAL INVESTIGATIONS AND THERAPEUTIC ASPECTS OF CHEMICALLY INDUCED TUMORS. (Ger.) Burkle, G. (Medizinisches Strahleninstitut der Universitat Tubingen, 7400 Tubingen, Rontgenweg 11, West Germany). *Fortschr. Geb. Roentgenstr. Nuklearmed.* 122(4):352-364; 1975. (82 references)

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3644 THE TOXICITY OF PLUTONIUM. (Eng.) Anonymous. *Medical Res. Council Report.* London, HMSO, 1975, 45 pp.

3645 PLUTONIUM PARTICLES: SOME LIKE THEM HOT. (Eng.) Lovins, A. B. (Friends of the Earth); Patterson, W. C. *Nature* 254(5498): 278-280; 1975. (No references)

3646 TUMOR VIRUSES (A BIBLIOGRAPHY WITH ABSTRACTS). (Eng.) Crockett, P. W. (Natl. Technical Information Service, Springfield, Va.). 75 pp., 1975. [available through National Technical Information Services, Washington D. C. Document No. NTIS/PS-75/263/4WJ].

3647 THE FELINE LEUKEMOGENIC AND SARCOMATOGENIC VIRUSES. (Fre.) Parodi, A. L. (Laboratoire d'Anatomie Pathologique, Ecole Nationale Veterinaire, 94701 Alfort, France). *C. R. Soc. Biol. (Paris)* 169(3/Suppl.):794-806; 1975. (89 references)

3648 VIROLOGY OF PROSTATIC CANCER. (Eng.) Sanford, E. J. (Pennsylvania State Univ. Coll. Medicine, Hershey, Pa. 17033); Rohner, T. J.; Rapp, F. *Cancer Chemother. Rep. (Part 1)* 59(1):33-38; 1975.

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3656 INTRAVASCULAR EVENTS IN CANCER DISSEMINATION: COAGULATION FACTORS [abstract]. (Eng.) Hilgard, P. (Essen Clin., W. Germany). *Eur. J. Cancer* 11(1):34; 1975. (5 references)

3657 INTRAVASCULAR EVENTS IN CANCER DISSEMINATION: SIGNIFICANCE OF VASCULAR DEVELOPMENT [abstract]. (Eng.) Hellmann, K. (Imp. Cancer Res. Fund, London, England). *Eur. J. Cancer* 11(1):36; 1975. (No references)

3658 INTRAVASCULAR EVENTS IN CANCER DISSEMINATION: THE SIGNIFICANCE OF CIRCULATING CANCER CELLS [abstract]. (Eng.) Salsbury, A. J. (Brompton Hosp., London, England). *Eur. J. Cancer* 11(1):37; 1975. (2 references)

3659 NEOPLASTIC DISEASE OF YAQUINA BAY BIVALVE MOLLUSKS. (Eng.) Mix, M. C. (Dept. General Science, Oregon State Univ., Corvallis, Ore.). *Cell Cycle in Malig. Immun., Proc. Annu. Hanford Biol. Symp., 13th.* Richland, Washington, D.C., U.S. Energy Research and Development Administration, 1975, pp. 369-386. (33 references)

3660 BENZENE RINGS AND THE BLADDER. (Eng.) Anonymous. *Lancet* 2(7931):402; 1975. (No references)

3661 THE IMPACT OF INDUCED MUTATIONS ON HUMAN POPULATIONS. (Eng.) Sutton, H. E. (Dept. Zoology, Univ. Texas at Austin, Austin, Tex. 78712). *Mutat. Res.* 33(1):17-24; 1975. (12 references)

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3663 VINYL CHLORIDE CARCINOGENESIS [abstract]. (Eng.) Duck, B. W. (B.P. Ltd., Sunbury on Thames, England). *Br. J. Cancer* 32(2):260; 1975. (3 references)

3664 VINYL CHLORIDE: HOW MANY UNKNOWN PROBLEMS? (Eng.) Haley, T. J. (Natl. Center for Toxicological Res., Jefferson, Ark. 72079). *J. Toxicol. Environ. Health* 1(1):47-73; 1975. (185 references)

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3666 METABOLIC AND BIOCHEMICAL CHANGES IN LEUKEMIA. (Eng.) Jaffe, N. (Harvard Medical School, Boston, Mass. 02115). *Mod. Probl. Paediatr.* 16:113-136; 1975. (114 references)

3667 MAMMALIAN PLASMA MEMBRANE. (Eng.) Bretscher, M. S. (Medical Res. Council Lab. Molecular Biology, Hills Road, Cambridge CB2 2QH, U.K.); Raff, M. C. *Nature* 258(5530):43-49; 1975. (84 references)

3668 TRANSLATIONAL STEP INHIBITED *IN VIVO* BY AFLATOXIN B_1 IN RAT-LIVER POLYSOMES. (Eng.) Sarasin, A. (Institut de Recherches Scientifiques sur le Cancer, Bôîte postale 8, F-94800 Villejuif, France); Moulé, Y. *Eur. J. Biochem.* 54(2): 329-340; 1975.

An attempt was made to localize the translational step inhibited *in vivo* by aflatoxin B_1 in rat liver cells. A simulation study was used to determine precisely the site inhibited *in vivo* after drug intoxication. It was based on two parameters: the kinetics of polysome labeling to follow the nascent peptide synthesis, and the kinetics of supernatant labeling to follow the completed protein synthesis. Wistar rats were given aflatoxin B_1 (1 mg/kg ip), followed by 12.5 µCi DL-(*carboxy*-^{14}C) leucine ip ten minutes before killing. Up to five hours after dosing, aflatoxin specifically inhibited the elongation and/or termination steps during protein synthesis; after longer periods of time, inhibition occurred essentially at the initiation step. When the intracellular concentration of aflatoxin was too high, particularly two hours after dosing, each step of protein synthesis was blocked. Polypeptide synthesis by the postmitochondrial supernatants isolated from aflatoxin-treated animals was impaired in the same proportion as protein synthesis *in vivo*. The damage caused by aflatoxin was mostly observed on microsomes. However, purified polysomes isolated from aflatoxin-treated rats synthesized proteins *in vitro* to the same extent as those from controls. These results suggest that aflatoxin metabolite(s) are bound to polysomes with noncovalent bonds. These active metabolites are probably lost during polysome isolation procedures. Early protein synthesis inhibition may be related to the carcinogenic properties of aflatoxin B_1.

3669 AFLATOXIN B_1 HYDROXYLATION: SENSITIVE MONOOXYGENASE MICROASSAY SUITABLE FOR LIVER BIOPSY SPECIMENS. (Eng.) Krieger, R. I. (Dept. Environmental Toxicology, Univ. California, Davis, Calif. 95616); Daine, K.; Hsieh, D. P. H.; Miller, J. L.; Thongsinthusak, T. *Res. Commun. Chem. Pathol. Pharmacol.* 12(2):287-296; 1975.

A method for measuring the rate of monooxygenase catalyzed hydroxylation of aflatoxin B_1 to aflatoxin Q_1 (AFQ) has been developed. It is suitable for use with small amounts of tissue obtained by needle or surgical biopsy of liver. Liver samples are homogenized in buffered saline containing a glucose-6-phosphate:NADPH generating system. ^{14}C-AFB is added to initiate a 10-min oxidation period. Quick-freezing stops oxidations, and AFB_1 and AFQ_1 are extracted using $CHCl_3$. After solvent removal, the residue is resuspended in benzene-acetonitrile (98:2) and applied to silica gel thin-layer chromatography plates, which are developed twice in chloroform-acetone-*n*-hexane (85:15:20). AFB_1 and AFQ_1 were located by fluorescence and scraped into vials for scintillation counting. The procedure resulted in a reaction which was linear for ten minutes using 5-10 mg liver tissue/0.2 ml incubation. Aflatoxin M_1 and three other metabolites more polar than AFB_1 were also produced. The apparent K_m for AFQ_1 formation was 8.6×10^{-4}M and V_{max} was 287 pM AFQ_1 mg protein^{-1} using bonnet monkey *Macaca radiata* liver. The procedures should be valuable in comparative biochemical studies, especially those using liver biopsy specimens of primates.

3670 DETOXIFICATION OF GROUNDNUT OIL. (Eng.) Shantha, T. (Central Food Technological Res. Inst., Mysore-570013, India); Murthy, V. S. *J. Food Sci. Technol.* 12(1):20-22; 1975.

The usefulness of different extractants (sodium chloride solution, sodium hydroxide, ammonia, and aqueous acetone) in removing aflatoxin from groundnut oil was investigated. The oil was mixed thoroughly with the extractant using an electrical stirrer and allowed to stand for phase separations. The aqueous and oil phases were collected separately for toxin estimation. Aflatoxin B_1 concentration in the groundnut oil samples tested ranged from 0.01-2.60 ppm. Eighty to ninety-five percent of the toxin present in the oil was removed by shaking it with either N/50 sodium hydroxide or aqueous sodium chloride or acetone. The emulsion formed by these extractants, however, made oil separation incomplete, thus affecting its recovery. Studies were undertaken to standardize ideal conditions for maximum removal of aflatoxin from the oil using acetone and sodium chloride solution. Although 70% acetone is widely used for toxin extraction in aflatoxin analysis, the high cost of acetone and its flammability limit its use in commercial practice. Retention of acetone and its odor by the treated oil is another serious problem that limits its usefulness. Extraction with 10% sodium chloride solution was determined to be the ideal process for removing about 85% of the toxin, with least emulsion problems and maximum oil recovery. Heating gives more efficient toxin extraction as well as reducing the viscosity of the oil and minimizing the emulsion losses.

3671 AFLATOXIN CAN BE DEGRADED BY THE MYCELIUM OF *ASPERGILLUS PARASITICUS*. (Eng.) Shih, C.-N. (Dept. Food Science and Food Res. Inst., Univ. Wisconsin-Madison, Madison, Wis. 53706); Marth, E. H. *Z. Lebensm. Unters. Forsch.* 158(6):361-362; 1975.

The degradation of aflatoxins by mycelium (aged 4, 8, or 16 days) of *Aspergillus parasiticus* was measured during 48-72 hr of incubation at 28 C in solutions at pH 2.5 and 6.0. The glucose-salt medium used contained approximately 315, 30, 155, and 20 µg aflatoxin B_1, B_2, G_1, and G_2, respectively, per 50 ml. The aflatoxins were degraded by the 8- and 16-day-old mycelium, but not by the 4-day-old mycelium. The 16-day-old mycelium degraded the toxins more repidly than did the 8-day-old mycelium. Degradation of toxin was similar at pH 2.5 and 6.0. These data indicate that the biological capacity of *A. parasiticus* mycelium changes as the mold matures.

3672 ACTION OF ALLOXAN ON THE MULTIPLICATION OF DIFFERENT TYPES OF NORMAL AND TUMOR CELLS, AND ON CHICKEN EMBRYO FIBROBLAST TRANSFORMATION BY ROUS VIRUS IN VITRO. (Fre.) Grobon, P. (Laboratoire de Radio-biologie, Faculté des Sciences, 91400 Orsay, France). *C. R. Acad. Sci. [D] (Paris)* 280(20):2413-2416; 1975.

The effect of alloxan was studied on *in vitro* growth of normal fibroblasts from 11-day old chick embryos and human lung embryos and the neoplastic cells of the C13/8 sub-clone of the BHK21, HeLa and virus-induced hamster sarcoma HS 5 cell lines. Rous chicken cell transformation by the Schmidt-Ruppin Rous sarcoma virus (SR-RSV) in the presence of alloxan was also observed. Fibroblasts from chick embryo skeletal muscle were cultured in plasma and Ringer's solution. Chick embryo fibroblasts from the ELB cell line and human lung embryo cells from the W 38 line were cultured in single cell layers. Alloxan, 250-350 µg/ml, did not inhibit growth of normal cells observed at 24, 48, and 72 hr. Concentrations above 0.25 mg/ml destroyed the cultures. HeLa cells were cultured in a hydrolysate of casein. By the third day of culture, 250 µg/ml of alloxan had destroyed all HeLa cells whether cell growth was confluent or nonconfluent. Similar toxic activity of alloxan was seen in HS 5 cultures. ELB cells infected with SR-RSV were cultured and alloxan, 350 µg/ml, added to the culture (24 hr after inoculation with high infective dose of SR-RSV) strongly inhibited growth after 3 days. Doses of 250-400 µg/ml inhibited growth of colonies of SR-RSV-transformed cells in ELB cultures inoculated with low infective doses of virus. Alloxan has an inhibitory effect *in vitro* on the growth of cancer cells but does not affect normal cell growth. The compound also inhibits transformation of ELB fibroblast cells by Rous sarcoma virus.

3673 STUDIES CONCERNING THE HISTOTOXICITY OF ISOBUTYL-2-CYANOACRYLATE TISSUE ADHESIVE WHEN EMPLOYED AS AN ORAL HEMOSTAT. (Eng.) Greer, R. O., Jr. (Univ. Colorado Medical Center, Denver, Colo. 80220). *Oral Surg.* 40(5) :659-669; 1975.

A study was implemented to determine the effectiveness of isobutyl-2-cyanoacrylate (bucrylate) as an oral hemostat, its influence on sequential wound healing, and its potential as a carcinogen. Three groups of male and female Long-Evans Hooded Rats underwent deep (40 socket) and superficial (surface) aerosol placement of bucrylate to maxillary molar extraction sites. Bucrylate proved to be an effective oral hemostat, rapidly retarding postextraction hemorrhage. Deep placement of the adhesive resulted in retarding of healing and lingering macrohistiocytic aggregates in wounds. Superficial placement of the material resulted in very little long-term macrohistiocytic response, and wound healing showed little retardation. No evidence of neoplasia were detected throughout the 9-mo period of observation, from histologic examination of specimens taken at complete necropsy.

3674 CYTOTOXICITY OF CARCINOGENIC AROMATIC AMIDES IN NORMAL AND XERODERMA PIGMENTOSUM FIBROBLASTS WITH DIFFERENT DNA REPAIR CAPABILITIES. (Eng.) Maher, V. M. (Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, Mich. 48201); Birch, N.; Otto, J. R.; McCormick, J. J. *J. Natl. Cancer Inst.* 54(6):1287-1294; 1975.

The effect of exposure to UV irradiation or to the *N*-acetoxy-ester derivatives of four carcinogenic aromatic amides (4-acetylaminobiphenyl (AABP), 2-acetylaminofluorene (AAF), 2-acetylaminophenanthrene, and 4-acetylaminostilbene) on cell survival was compared in strains of cultured human fibroblasts possessing normal rates of excision repair of DNA and in three strains of xeroderma pigmentosum (XP) cells, each differing in its rate of excision repair. These fibroblasts (XP2BE, XP4BE, XP12BE, and XP13BE) were derived from skin of XP patients. The slope of the survival curve for the XP strain with the poorest capacity for excision repair after UV exposure (XP-12BE complementation group A) was 5.8-fold steeper than the exponential portion of the curve for the normally repairing strains; that of XP2BE (complementation group C) was 1.95-fold; and that of XP4BE (a variant capable of a normal rate of dimer excision) was only 1.3-fold steeper. The slope of the survival curves after exposure to each *N*-acetoxy ester derivative for these same XP strains averaged 6.4, 2.0, and 1.4 times steeper, respectively, than that of the normal strains tested. The excision repair capacity of these lines after exposure to *N*-acetoxy-AAF (50 µM/ml) was tested with alkaline cesium chloride density gradient centrifugation to detect incorporation of tritiated thymidine into nonreplicated DNA. The normal strains and XP4BE exhibited DNA excision repair, whereas XP patients 2 and 12 did not. The cytotoxic effect of the four parent aromatic amide carcinogens and some of their derivatives, in the XP2BE strain, was compared with their effect on the normal fibroblasts. The parent amides proved to be noncytotoxic, while the *N*-hydroxy derivatives of each aromatic amide were highly cytotoxic, as were the ester compounds. For each active derivative, the slope of the survival curve for XP2BE was 2-2.5 times steeper than that of the normally repairing strain.

3675 ACTIVATION OF CARCINOGENIC ARYLHYDROXAMIC ACIDS BY HUMAN TISSUES. (Eng.) King, C. M. (Michael Reese Hosp. and Medical Center, 29th St. and Ellis Ave., Chicago, Ill. 60616); Olive, C. W.; Cardona, R. A. *J. Natl. Cancer Inst.* 55(2):285-287; 1975.

The abilities of cytosols of human tissues obtained at surgery or autopsy to promote the introduction of the arylamine moiety of *N*-hydroxy-*N*-2-fluorenylacetamide or *N*-hydroxy-*N*-4-biphenylacetamide into tRNA were determined. Incubation of the arylhydroxamic acids (0.042 µM) and tRNA with 105,000 x g supernatants of homogenates of small intestine, liver, or colon led to formation of arylamine-substituted nucleic acid adducts. These results indicate that enzymes of human tissues can activate arylhydroxamic acids by *N*→*O* acyl transfer. The unstable *N*-acetoxyarylamines formed by these enzymes reacted spontaneously with the tRNA to give covalently linked adducts with the nucleic acid. Biphenylamine incorporation was only 17% of that of fluorenylamine un-

der conditions most favorable for adduct formation with the fluorene derivative. The activation of these arylhydroxamic acids demonstrates that an enzyme of human tissue can transform metabolites of carcinogenic arylamines into derivatives capable of covalent reaction with nucleic acids.

3676 GENETIC DIFFERENCES IN THE INDUCTION OF ARYL HYDROCARBON HYDROXYLASE AND BENZO[*a*]-PYRENE CARCINOGENESIS IN C3H/He AND DBA/2 STRAINS OF MICE. (Eng.) Watanabe, M. (Res. Inst. for Tuberculosis, Leprosy and Cancer, Tohoku Univ., Hirosemachi 4-12, Sendai 980, Japan); Watanabe, K.; Konno, K.; Sato, H. *Gann* 66(3):217-226; 1975.

The effects of 3-methylcholanthrene and 5,6- and 7,8-benzoflavones on aryl hydrocarbon (benzo[*a*]-pyrene) hydroxylase activity in the liver, small intestine, lung, and skin tissues from C3H/He and DBA/2 strains of mice under controlled lighting conditions were examined. The animals were kept in an environment in which the lights were on from 10 p.m. to 10 a.m. in a 24-hr cycle. 3-Methylcholanthrene and 5,6- or 7,8-benzoflavone were administered intragastrically at a dose of 1 mg in 0.1 ml of corn oil per 10 g body weight at 9 a.m. Apparent differences were observed in the inducibility of the hepatic enzyme by the inducers between the two strains of mice, showing that the enzyme in the C3H/He mice is inducible but not in the DBA/2 mice. Comparison of the results on the enzyme induction by 3-methylcholanthrene in the liver among the parent, intercrossed, and backcrossed mice suggested that the inducibility may be inherited as a single autosomal dominant trait. However, different genetic responses to 3-methylcholanthrene and benzoflavones in the enzyme of small intestine might be considered, because a discrepancy in the inducibility of the enzyme between the liver and the small intestine from the identical mice was demonstrated when the progeny of F_2 and (DBA/2 x F_1) backcross were used. On the other hand, no apparent difference was found in the inducibility of the enzyme in the lung and skin between the C3H/He and the DBA/2 mice. It is assumed that the genetic regulation of the induction of aryl hydrocarbon hydroxylase was separately controlled in the respective tissues from the identical mice. By the repeated topical applications of benzo[*a*]pyrene (100 nM/0.2 ml acetone), the incidence of skin cancer was higher in the DBA/2 mice (4.6%) than in the C3H/He mice (1.5%). The relationship between the induction of aryl hydrocarbon hydroxylase and carcinogenicity in the skin is discussed.

3677 THE AUTOXIDATION OF 6-HYDROXYBENZO[*a*]-PYRENE AND 6-OXOBENZO[*a*]PYRENE RADICAL, REACTIVE METABOLITES OF BENZO[*a*]PYRENE. (Eng.) Lorentzen, R. J. (Johns Hopkins Univ., Baltimore, Md., 21205); Caspary, W. J.; Lesko, S. A.; Ts'o, P. O. P. *Biochemistry* 14(18):3970-3977; 1975.

A labile metabolite of benzo(*a*)pyrene, 6-hydroxybenzo(*a*)pyrene, was autoxidized in aqueous buffer-ethanol solutions to produce three stable diones (6,12-benzo(*a*)pyrene dione, 1,6-benzo(*a*)pyrene dione, and 3,6-benzo(*a*)pyrene dione) and a small amount of an unidentified paramagnetic, violet-colored material. In this reaction, oxygen was reduced to hydrogen peroxide and probably to other reactive reduced oxygen species. A free radical derived from 6-hydroxybeno(*a*)pyrene by one-election oxidation 6-oxobenzo(*a*)pyrene radical, was apparently an obligatory intermediate in this autoxidation, as indicated by its kinetics of formation and decay. This free radical could also be produced quantitatively in benzene by oxidation of 6-hydroxybenzo(*a*)pyrene with aqueous $K_3Fe(CN)_6$ and isolated in the absence of oxygen. Like 6-hydroxybenzo(*a*)pyrene, this isolated free radical was autoxidized in aqueous buffer-ethanol solutions and yielded identical products. 6-Hydroxybenzo(*a*)pyrene was also oxidized rapidly in rat liver homogenates to the three benzo(*a*)pyrene diones, indicating that it is a labile precursor of these often-found products of benzo(*a*)pyrene metabolism. The production of reactive hydrocarbons and reduced oxygen intermediates may explain the results of previous studies that demonstrated that 6-hydroxybenzo(*a*)pyrene binds covalently to, and causes strand breakage, in nucleic acids. This reactivity of 6-hydroxybenzo(*a*)pyrene may also be related to its high toxicity toward cells in culture and its ability to morphologically transform Syrian hamster embryo fibroblasts.

3678 MUTAGENICITY OF NON-K-REGION DIOLS AND DIOL-EPOXIDES OF BENZ(a)ANTHRACENE AND BENZO(a)PYRENE IN *S. TYPHIMURIUM* TA 100. (Eng.) Malaveille, C. (International Agency for Res. on Cancer, 150 cours Albert Thomas, 69008 Lyon, France); Bartsch, H.*; Grover, P. L.; Sims, P. *Biochem. Biophys. Res. Commun.* 66(2):693-700; 1975.

The mutagenicity of a series of benzo(a)pyrene and benz(a)anthracene derivatives toward *Salmonella typhimurium* strain TA 100 was examined using a tissue-mediated assay. Groups of three female BD-VI rats received one ip injection of 3-methylcholanthrene (40 mg/kg) two days before they were killed. Post-mitochondrial 9,000 x *g* supernatants were prepared from pooled rat liver by centrifugation of an homogenate (3 ml 0.15 M KCl/g liver). Supernatant, cofactors ($NADP^+$ and glucose 6-phosphate), bacteria and the substrate were combined in a soft agar layer and plated onto histidine-deficient media. K-region epoxides and diol-epoxides were assayed for mutagenicity to TA 100 directly in the absence of any metabolic activation system. When incubated with rat liver supernatant, benzo(a)pyrene 7,8-diol and benz(a)anthracene 8,9-diol were more active than the parent hydrocarbons in inducing *his* revertant colonies of TA 100. Benzo(a)pyrene 9,10-diol was less active than benzo(a)pyrene; the K-region diols, benz(a)anthracene 5,6-diol and benzo(a)pyrene 4,5-diol, were inactive. None of the diols was active when the cofactors for the microsomal monooxygenase were omitted. The diol-epoxides benzo(a)pyrene 7,8-diol 9,10-oxide, benz(a)anthracene 8,9-diol 10,11-oxide and 7-methylbenz(a)anthracene 8,9-diol 10,11-oxide and the K-region epoxides, benzo(a)pyrene 4,5-oxide and benz(a)anthracene 5,6-oxide, were mutagenic without further metabolism.

3679 FREE RADICAL EVOLUTION IN RAT LIVER FOLLOWING THE INGESTION OF DAB. (Eng.) Duchesne, J. (Dep. At. Mol. Phys., Univ. Liege, Belgium); Goutier, R.; Marechal, R.; Van De Vorst, A. *Phys. Med. Biol.* 20(2):305-309; 1975.

The effect of the ingestion of 4-dimethyl-aminoazobenzene (DAB) on the density and distribution of organic free radicals in rat liver was studied by electron spin resonance. Forty-five 7-mo-old J013 male albino rats were fed daily 10 g of boiled rice and raw carrots mixed with 0.2 g medicinal oil and 6 mg DAB; 45 control rats received the same diet without DAB. Electron spin resonance measurements were made on liver removed 5, 10, 20, 30, 100, 120, 130, 140, 150, and 200 days after the beginning of ingestion, using three samples each from the right and left lobes for each animal. The content of free radicals was obtained by double integration of the spectra. A line intensity decrease of 30% was detected in the DAB-fed rats as early as 5 days after intake. The decrease continued for 150 days, when a tumor was first observed. Four samples taken from points equally spaced from the edge of the lobe to the vicinity of the tumor gave a signal intensity of 50% around the extremity, which gradually decreased to 20% for the sample taken close to the tumor, indicating a progressive decrease in the number of free radicals. Measurements made between 150 and 200 days, when the tumor was large enough for observation, did not reveal any signals. Since the free radicals involved are concentrated largely in mitochondria, it is suggested that the changes observed during carcinogenesis are consistent with biochemical observations made on isolated mitochondria. This study also indicates the value of electron spin resonance spectra determinations in some aspects of carcinogenesis research.

3680 7,12-DMBA-INDUCED RAT MAMMARY TUMOUR STUDIED FOR HORMONAL RESPONSIVENESS *IN VITRO*. 1. SHORT-TERM INCUBATIONS OF CELL SUSPENSIONS. (Eng.) Aspegren, K. (Dept. Surgery, Univ. Lund, Sweden). *Acta Pathol. Microbiol. Scand.* [*A*]. 83(1):25-36; 1975.

The effect of testosterone, progesterone, and 17-β-estradiol on the incorporation of tritiated thymidine into DNA was studied *in vitro* using cell suspensions from 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat mammary carcinomas and subcutaneous sarcomas. The mammary tumors were induced in female Sprague-Dawley rats by intragastric instillation of 20 mg DMBA, while sarcomas were induced by s.c. injection of 0.4 mg of methylcholanthrene or 2 mg DMBA. Cell suspensions were labeled with either 2 μCi H^3-thymidine or 2 μCi 5-H^3-uridine. In one series of experiments cells were incubated with testosterone at 0.5, 5, and 50 μg/ml; progesterone at 0.8, 8, and 80 μg/ml; or 17-β-estradiol at 0.02, 0.2, 2, and 20 μg/ml concentrations. In another series, testosterone, progesterone, 17-β-estradiol, 17-α-estradiol, and cholesterol were used at concentrations of 20, 50, and 80 μg/ml. Both stimulatory and inhibitory effects of the hormones were seen. The two types of tumor reacted similarly. Cholesterol had no effect on the incorporation of H^3-thymidine into DNA, whereas 17-β-estradiol was a strong inhibitor at 20 μg/ml. Progesterone and testosterone gave about half the effect of 17-β-estradiol, whereas 17-α-esteradiol had a smaller but significant effect. It is concluded that hormonal responsiveness *in vitro* may not mirror actual hormonal responsiveness *in vivo* of DMBA-induced mammary tumor in the rat.

3681 CARCINOGENICITY OF 6-AMINOCHRYSENE IN MICE. (Eng.) Lambelin, G. (Cont. Pharma Res. Lab., Machelen, Belgium); Roba, J.; Roncucci, R.; Parmentier, R. *Eur. J. Cancer* 11(5):327-334; 1975.

The carcinogenicity of 6-aminochrysene was studied in mice. Bioavailability studies were conducted in 60 male CFLP mice. 6-Aminochrysene (5 mg) was administered either p.o. or topically. Four groups of 10 animals each were used for the determination of the 0/48 hr ^{3}H-urinary excretion after single skin application of the ointment to either the dorsal or ventral skin, with or without a collar which prevented the animals from licking up the ointment. Two other groups of ten animals each received the compound by stomach tube; one group received it as 1% tragacanth gum mucilage (0.3 ml/animal), and the other received it in the ointment form. The assay of unchanged compound was performed by gas liquid chromatography. Urinary excretion was about twice as high after skin application (4.19-7.58% of the dose administered) than after p.o. administration (1.85-3.32% of the dose administered). Three hundred SPF CFLP strain mice were then used in carcinogenicity studies. About 100 mg of an ointment containing 5% 6-aminochrysene was rubbed daily on either the dorsal or ventral skin. Mice were examined regularly for skin lesions. Half of the mice were treated for six months; the others were treated for an additional three months. Benign skin tumors developed after three months and skin malignancies developed after seven months. Primitive cutaneous tumors arose at the site of application and other lesions arose elsewhere on the skin and in the viscera. Gross and histopathological examination revealed that 92% of mice in the 6-aminochrysene-treated groups had tumors, compared to 6% and 5%, resp. in vehicle-treated and untreated controls. In the 6-aminochrysene treated mice, lung tumors were observed in 71% of the animals and liver lesions in 38%. Female mice responded earlier than males. Induction of skin tumors was more rapid when 6-aminochrysene was applied ventrally rather than dorsally. The bioavailability studies indicate that the bioavailability of 6-aminochrysene is low and that skin absorption of the compound is more effective than oral absorption. Like the other polycyclic hydrocarbons, 6-aminochrysene exhibits a carcinogenic activity in mice.

3682 SPECIFIC CRYSTAL STRUCTURES OF CARCINOGENIC HYDROCARBONS. (Ger.) Contag, B. (Fachbereich Chemie, Technische Fachhochschule Berlin, West Germany). *Naturwissenschaften* 62(9): 434-435; 1975.

All of 14 carcinogenic polycyclic hydrocarbons stu-

died showed a particular two-dimensional structure of specific crystal faces. Examples are: benz[a]-anthracene, benzo[a]pyrene, 3-methylcholanthrene, dibenz[a,h]acridin, and benzo[g,h,i]perylene. None of 15 similar but noncarcinogenic compounds demonstrated this specific structure. The significance of this structural pattern is envisaged as a matrix for the specific two-dimensional adsorption of biogenic macromolecules. It is assumed that this specific adsorption may be the primary reaction of these carcinogenic compounds.

3683 CHROMATOGRAPHIC ANALYSES OF 3-METHYLCHOLANTHRENE METABOLISM IN ADULT AND FETAL MICE AND THE OCCURRENCE OF CONJUGATING ENZYMES IN THE FETUS. (Eng.) Takahashi, G. (Chest Dis. Res. Inst., Kyoto Univ., Japan); Yasuhira, K. *Cancer Res.* 35(3): 613-620; 1975.

Metabolites of 3-methylcholanthrene (3MC) were studied in adult and fetal DDD strain mice after i.v. injection of ^{3}H-3MC or ^{14}C-3MC. Sephadex LH-20 chromatography yielded three groups of metabolites: one unidentified, one containing the hydrocarbon and hydroxylated derivates, and one consisting of conjugated metabolites. The latter was further separated into a fraction susceptible to the action of β-glucuronidase (and to a lesser extent arylsulfatase) and a fraction resistant to these enzymes but completely acid-hydrolyzable. The enzyme-resistant conjugates predominated in brain, muscle, and lung, while those sensitive to the enzymes predominated in kidney, liver, and bile in adult mice. In fetal mice, the enzyme-resistant conjugates were more characteristic of the early stages of development, while the enzyme-labile conjugates in kidney, liver, and intestinal tract increased as fetuses approached term. Since conjugated metabolites of 3MC did not cross the placental barrier (although 3MC and nonconjugated metabolites did) it is concluded that hydrolases and conjugases are active in fetal mouse tissues.

3684 CARCINOGENICITY OF THREE DOSE LEVELS OF 1,4-BIS(4-FLUOROPHENYL)-2-PROPYNYL-*N*-CYCLOOCTYL CARBAMATE IN MALE SPRAGUE-DAWLEY AND F344 RATS. (Eng.) Weisburger, E. K. (Natl. Cancer Inst., Bethesda, Md.); Ulland, B. M.; Schueler, R. L.; Weisburger, J. H.; Harris, P. N. *J. Natl. Cancer Inst.* 54(4):975-979; 1975.

1,4-Bis(4-fluorophenyl)-2-propynyl-*N*-cycloactyl carbamate (FPOC) was incorporated into the diet of male Sprague-Dawley and F344 rats at 125, 250 and 500 ppm in order to determine if lower doses permitted longer survival and greater incidence of intestinal carcinomas. The animals were fed the diet continuously for the first four wk; the protocol was then changed to three wk of compound administration followed by one wk of basal diet and this cycle was repeated every fourth wk. The experiment was terminated at 30 wk in F344 rats and at 42 wk in Sprague-Dawley rats. The entire gastrointestinal tract was examined at complete necropsy. F344 male rats developed scirrhous, papillary and cystic mucinous carcinoma in the small intestine. Mortality in high dose groups was attributed to dose-related chronic glomerolonephritis. Intestinal tumors in the Sprague-Dawley rats were similar to those of F344 except for two colon carcinomas. Mammary tumors, cystic and papillary adenocarcinomas were observed. Hematopoietic neoplasia developed in Sprague-Dawley rats and hepatocellular carcinomas were observed in one control and two experimental Sprague-Dawley rats. After FPOC feedings, a 68% survival rate occurred in Sprague-Dawley rats after 18 wk and no F344 rats lived after 12 wk. A high incidence of adenocarcinoma in mammary glands of Sprague-Dawley males is induced by FPOC. Using a lower dose of FPOC does not permit longer survival or higher incidence of tumors.

3685 THE METABOLISM OF ETHIONINE IN RATS. (Eng.) Brada, Z. (Papanicolaou Cancer Res. Inst., Miami, Fla. 33136); Bulba, S.; Cohen, J. *Cancer Res.* 35(10):2674-2683; 1975.

The L-[*ethyl*-1-^{14}C]ethionine metabolites soluble in trichloroacetic acid were studied in female CFN rats by the use of column chromatography. After po application of 12.5 mg/100 g ethionine, its absorption from intestinal lumen was rapid, and about 60% was absorbed within 90 min. Any unabsorbed ethionine was later excreted in the feces. During the passage through the gastrointestinal tract, a portion of ethionine was metabolized. The fate of absorbed ethionine was investigated in the small intestine, liver, blood, kidney, and urine as a function of time after application. A great part of ethionine was quickly oxidized to ethionine sulfoxide. In liver and kidney, the concentration of ethionine sulfoxide was higher than that of free ethionine. In all organs, the presence of *N*-acetylethionine sulfoxide was also demonstrated. Ethionine sulfoxide can be reduced, and *N*-acetylethionine can be deacetylated *in vivo* as demonstrated by the formation of *S*-adenosylethionine from ethionine sulfoxide and *N*-acetylethionine. In urine, four main components were observed: *N*-acetylethionine sulfoxide, *S*-adenosylethionine, ethionine sulfoxide, and free ethionine. Some minor unidentified components were also present in the urine and in different organs. The probable site of origin of urinary *S*-adenosylethionine is the kidney.

3686 MUTAGENICITY *IN VITRO* AND POTENTIAL CARCINOGENICITY OF CHLORINATED ETHYLENES AS A FUNCTION OF METABOLIC OXIRANE FORMATION. (Eng.) Greim, H. (Dept. Toxicology of Gesellschaft fur Strahlenund Umweltforschung, 8042 Munchen-Neuherberg, West Germany); Bonse, G.; Radwan, Z.; Reichert, D.; Henschler, D. *Biochem. Pharmacol.* 24(21): 2013-2017; 1975.

The mutagenicity of six chlorinated ethylenes formed during microsomal activation was tested in a metabolizing *in vitro* system with *Escherichia coli* K_{12}. Mutation rates were determined for three back mutation systems gal+, arg+, and nad+, and for the MTR system where forward mutation leads to resistance to 5-methyl-DL-tryptophan. Cells were incubated

for two hours with microsomal protein from mouse liver, an NADPH-generating system with 5 μM $MgCl_2$, and various concentrations of the test compounds: etrachloroethylene, trichloroethylene (TRI), 1,1-dichloroethylene (1,1-DCE), cis-1,2-dichloroethylene, rans-1,2-dichloroethylene, and vinyl chloride (VCM). Only those compounds (VCM, 1,1-DCE, and TRI) that form very unstable oxiranes induced mutations in the test system. The highest mutation rates were detected in the arg+ system; the other systems were ess sensitive to the mutagenic effects of the metaolites. The mutagenicity of TRI was unexpected, nd further study of the mutagenic and potentially arcinogenic properties of this compound are recomended.

687 EFFECTS OF PROLONGED ETHYLENE THIOUREA INGESTION ON THE THYROID OF THE RAT. Eng.) Graham, S. L. (Bureau of Foods, Food and rug Administration, Washington, D.C. 20204); Davis, . J.; Hansen, W. H.; Graham, C. H. *Food Cosmet. oxicol.* 13(5):493-499; 1975.

ive groups of 68 male and 68 female Charles River ats, approximately five weeks old, were fed ethyene thiourea (ETU) for two years at levels of 0, , 25, 125, 250 or 500 ppm in the diet. Body weights, e weights of the thyroid and other organs, thyroil uptake of ^{131}I, hematology, and histology were e criteria studied. ETU was found to be a thyroid rcinogen for the rat at the 250 and 500 ppm dietary vels and a thyroid tumorigen at the 125 ppm level; caused a slight thyroid hyperplasia at the 5 and ppm feeding levels. Thyroid hyperplasia was not ticeably reversible in those rats in each group at were changed to control diet after 66 wk on U diets. ETU ingestion at the 5 and 25 ppm levels s not biologically deleterious to the rat. The ta support the view that ETU-induced thyroid neoasia in the rat are the result of excessive pharcological stimulation, i.e., they occur because excessive endocrine organ stimulation and not cause of the reaction of one molecule of carcinon with one cell to initiate neoplasia.

88 PROLACTIN AND GROWTH HORMONE LEVELS IN DIFFERENT INBRED STRAINS OF MICE: PATTERNS ASSOCIATION WITH ESTROUS CYCLE, TIME OF DAY, PERPHENAZINE STIMULATION. (Eng.) Sinha, Y. N. iv. Diabetes and Endocrinology, Scripps Clinic Res. Foundation, La Jolla, Calif. 92037); locks, C. B.; VanderLaan, W. P. *Endocrinology* (5):1112-1122; 1975.

olactin (PRL) and growth hormone (GH) secretion strains of mice with varying incidences of mamy tumors and after stimulation with perphenazine e compared. Pituitary concentrations of PRL and uitary and serum concentrations of GH were genlly higher in strains with high incidence of mary tumors. Basal PRL levels in serum samples little correlation with the incidence of mamy tumors in different strains. However, PRL centrations in sera after perphenazine (1 μg/g, followed the mammary tumor incidence rate of strain: C3H/St and CBA/St, the two high-incidence strains, had maximum PRL levels of about 200 ng/ml; C57BL/ST and BALB/cST, the two low-incidence strains, had about 600 ng/ml; and DBA/2St, the medium-incidence strain, had an intermediate level. The rate of metabolism of PRL in strains with high incidence of mammary tumors may be faster than in those with low incidences. Perphenazine had no influence on GH secretion in most mice. The strain-specific differences in PRL and GH concentrations were usually present even during cyclical and diurnal fluctuations. Serum PRL and GH levels were generally higher during the follicular phase and lower during the luteal phase of the estrous cycle in both C3H/St and C57BL/St strains. It is possible that these strain-specific differences may be an important factor in the development of mammary tumors.

3689 *IN VITRO* STIMULATION OF HUMAN BREAST TISSUE BY HUMAN PROLACTIN. (Eng.) Dilley, W. G. (Coll. Physicians Surg., Columbia Univ., New York, N.Y.); Kister, S. J. *J. Natl. Cancer Inst.* 55(1):35-36; 1975.

The growth effects of insulin, ovine prolactin, and human prolactin on four-day cultures of normal breast tissue from 30 women were studied. All hormones were used at 5 μg/ml. Eight hours before termination, colchicine (0.1 μg/ml) or ^{3}H-thymidine (1 μCi) was added to each culture, and mitotic figures or labeled cells were counted in histologic sections. Although the epithelium survived four days in culture, there was little mitosis or DNA synthesis in the absence of hormones *in vitro*. Insulin increased the mitotic activity of cultures by 390% and the further addition of human prolactin resulted in a 36% increase in activity over that obtained with insulin alone. The addition of ovine prolactin caused only a minimal increase in the insulin-induced mitotic activity. These results suggest that maximal effects on normal human breast tissue can be obtained with human hormones; further studies to specify the carcinogenic function of prolactin *in vitro* on human tissue should use human prolactin.

3690 INCREASED RISK OF ENDOMETRIAL CARCINOMA AMONG USERS OF CONJUGATED ESTROGENS. (Eng.) Ziel, H. K. (4900 Sunset Blvd., Los Angeles, Calif. 90027); Finkle, W. D. *N. Engl. J. Med.* 293(23): 1167-1170; 1975.

The possibility that the use of conjugated estrogens increases the risk of endometrial carcinoma was investigated in patients and a two-fold age-matched control series from the same population. Conjugated estrogens (principally sodium estrone sulfate) use was recorded for 57% of 94 patients with endometrial carcinoma, and for 15% of controls. The corresponding point estimate of the (instantaneous) risk ratio was 7.6 with one-sided 95% lower confidence limit of 4.7. The risk-ratio estimate increased with duration of exposure: from 5.6 for 1 to 4.9 yr exposure to 13.9 for seven or more years. The estimated proportion of cases related to conjugated estrogens, the etiologic fraction, was 50% with a one-sided 95% lower confidence limit

of 41%. These data suggest that conjugated estrogens have an etiologic role in endometrial carcinoma.

3691 CARCINOGENICITY OF THE ANTINEOPLASTIC AGENT, 5-(3,3-DIMETHYL-1-TRIAZENO)-IMIDAZOLE-4-CARBOXAMIDE, AND ITS METABOLITES IN RATS. (Eng.) Beal, D. D. (St. Vincent Hosp., Worcester, Mass.); Skibba, J. L.; Croft, W. A.; Cohen, S. M.; Bryan, G. T. *J. Natl. Cancer Inst.* 54(4):951-957; 1975.

The carcinogenicities of the antineoplastic agent, 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC), and its metabolites 5-(3-methyl-1-triazeno)-imidazole-4-carboxamide (MTIC), 5-aminoimidazole-4-carboxamide (AIC), 2-azahypoxanthine (2-AH), and 5-diazoimidazole-4-carboxamide (Diazo-ICA) were studied. Test animals including weanling Sprague-Dawley rats and female Buffalo rats were fed diets supplemented with DTIC (346-974 mg/rat) and DTIC metabolites. Cumulative doses were: 9.5-435 mg/rat Diazo-ICA; 601 mg/rat 2-AH; and 1-890 mg/rat MTIC. DTIC-induced thymic and mammary tumors were injected sc and ip, respectively, into female Sprague-Dawley rats. Male Sprague-Dawley rats were given ^{14}C-DTIC-2 (6 µCi) or ^{14}C-DTIC-methyl (10 µCi) ip prior to analysis of feces, urine and expired CO_2 to determine ^{14}C retention over eight hours. Rats fed DTIC developed tumors of the mammary gland, thymus and spleen. Animals fed a cumulative dose of 740 mg/rat/14 wk DTIC developed a 100% incidence of mammary adenocarcinomas and thymic lymphosarcomas within 18 wk. Both thymic and mammary tumors were transplantable. Metabolites of DTIC-Diazo-ICA pathway were not active. MTIC (890 mg/rat/14 wk) caused a high incidence (13/16) of mammary adenofibromas and a low incidence of leiomyosarcomas of the uterus (3/16); this was not altered by single or multiple ip injections. Twenty animals fed 2-AH (601 mg/rat/21 wk) developed three mammary adenocarcinomas and one adrenal cortical adenoma. Twenty rats fed AIC (1,278 mg/rat/21 wk) developed various malignant tumors. DTIC induced thymic lymphosarcomas in greater than 90% incidence after feeding, and 44% incidence after a single ip injection (400 mg/kg). It also induced a 50% incidence of mammary adenocarcinomas in male Sprague-Dawley rats within 18 wk. No correlation was found between DTIC uptake by a given organ and its susceptibility to tumors. These studies show that none of DTIC's metabolites are as carcinogenic as DTIC alone. Because the data show carcinogenic properties of DTIC resembling those of carcinogenic *N*-nitroso compounds, these may have similar mechanism(s) of action.

3692 MEGALOCYTOSIS AND OTHER ABNORMALITIES EXPRESSED DURING PROLIFERATION IN REGENERATING LIVER OF RATS TREATED WITH METHYLAZOXYMETHANOL ACETATE PRIOR TO PARTIAL HEPATECTOMY. (Eng.) Zedeck, M. S. (Memorial Sloan-Kettering Cancer Center, New York, N. Y. 10021); Sternberg, S. S. *Cancer Res.* 35(8):2117-2122; 1975.

The effect of a single dose of methylazoxymethanol acetate on regenerating liver cells was studied in male SD rats. Methylazoxymethanol acetate (35 mg/kg) in normal saline was injected iv into 4-wk-old animals, which were partially hepatectomized seven days later. At 20 and 28 hr after surgery, the hepatocytes (and their nuclei) of treated rats were larger than those of untreated rats. By 48 hr, nearly all hepatocytes of treated rats were megalocytic. At 72 and 96 hr, changes in liver architecture were found. No changes were found in the controls. At 3-4 mo, most changes were reversed. Mitotic indices of hepatocytes were less in treated *vs* untreated rats at 28 hr, but were higher by day 2-14. At 28 hr, eight of ten rats showed abnormal mitotic figures. The percentage of abnormal mitoses at 28, 48, and 96 hr were 16.2, 11.1, and 19.5%, respectively, in treated rats and 0.15, 0.7, and 0.43% in control rats, respectively. Rats that were partially hepatectomized eight weeks after injection showed 6.5% abnormal mitoses at 48 hr. Seven 3-mo-old rats were given the same treatment as the original group. The livers of each showed 2/3 of the hepatocytes to be enlarged, and 50% abnormal mitoses. Another five rats were treated similarly, and autopsy at eight months disclosed neither hyperplasia nor carcinoma. At 20 hr after surgery [*methyl*-^{3}H]TdR incorporation was significantly less in the treated rats. At 48 hr, when control levels were decreasing, those of treated rats were maximum and were significantly higher at four and seven days. Total liver DNA, RNA, and protein synthesis were also significantly reduced in treated *vs* control rats. The results suggest that methylazoxymethanol acetate causes a reduction in the number of regenerating cells after partial hepatectomy. The presence of megalocytes and abnormal mitoses do not seem to result in increased incidence of tumors. The latent effects of the carcinogen appear to be long lasting and are evident in regenerative proliferation.

3693 ENZYMATIC FORMATION OF CHEMICALLY REACTIVE METABOLITES OF *N*-NITROSO-DESMETHYL TRIPELENNAMINE BY A MECHANSIM OTHER THAN *N*-DEALKYLATION. (Eng.) Rao, G. S. (Building 10, Room 8N-107, Natl. Heart Lung Inst., Bethesda, Md. 20014); Krishna, G.; Gillette, J. R. *Biochem. Pharmacol.* 24(18):1707-1711; 1975.

Benzyl-^{14}C and *N*-methyl-^{3}H labeled *N*-nitroso derivatives (NDT) of tripelennamine were synthesized by reacting the corresponding labeled parent drug with sodium nitrite at pH 1-2, and their covalent binding to rat liver microsomes was compared with that of radiolabeled tripelennamine. Liver microsomes were prepared from 10,000 x *g* supernatants of liver homogenates from male Sprague-Dawley rats by a calcium precipitation method. The covalent binding of these substances is mediated by liver microsomal cytochrome P-450 enzymes; it required an NADPH-generating system and oxygen, and was inhibited by $CO:O_2$ (8:2). Reduced glutathione (1 mM) also inhibited the covalent binding. The covalent binding of NDT to liver microsomal proteins from phenobarbital-pretreated rats (80 mg/kg, ip daily for three days) was ten times greater than that of tripelennamine. A K_m of 60 µM and a V_{max} of 1 nM/mg of protein/min were obtained for the covalent

binding of NDT. Phenobarbital and acetone (2.5 m/kg po) pretreatments of rats increased covalent binding of both the drug and its nitroso derivative, while pretreatment with 3-methylcholanthrene (40 mg/kg ip daily for three days) decreased their binding. These results suggest that chemically reactive intermediates of tripelennamine and NDT are involved in the covalent binding. Under the *in vitro* conditions employed, the rate of *N*-demethylation of NDT was lower than that of the parent drug. Moreover, the covalent binding of the *N*-methyl-^{3}H labeled nitroso derivative was equivalent to that of the benzyl-^{14}C labeled derivative. Thus, *N*-demethylation is not a requisite for the covalent binding of tripelennamine and its *N*-nitroso derivative. The mechanism of the covalent binding of the *N*-nitroso derivative of tripelennamine, therefore, differs from that of dimethylnitrosamine.

3694 TUMOR-INDUCING EFFECT OF TRINITROSO-TRIMETHYLENE-TRIAMINE (TTT) WHEN ORALLY APPLIED IN DIMETHYLSULPHOXIDE (DMSO) FOR SOLVENT. (Eng.) Urban, H. (Friedrich-Schiller-Universitat, Pathologisches Institut, 69 Jena, Ziegelmuhlenweg 1, East Germany); Amlacher, E.; Danz, M. *Exp. Pathol. (Jena)* 10(5/6):364-365; 1975.

The effects of trinitroso-trimethylene-triamine (TTT) dissolved in dimethylsulfoxide (DSMO) were studied in 20 rats (Wistar, female). After 362 days of dosage with TTT in DSMO (ip or po; total dose 172 mg/rat) angiomatous structures were found in the livers of 5 rats. After 459 days liver adenomas were found in two moribund rats.

3695 DEOXYRIBONUCLEASES AND NUCLEIC ACID CONTENT OF RAT LIVER UNDER THE INFLUENCE OF SINGLE TOXIC DIETHYLNITROSAMINE DOSES. (Eng.) Hollatz, R. (Institut fur Pharmakologie, Toxikologie und Pharmazie der Tierarztlichen Fakultat der Universitat, Koniginstrasse 16, D-8 Munchen 22, West Germany); Tempel, K.; Wulffius, M. *Experientia* 31(1):87-88; 1975.

The effects of diethylnitrosamine (DENA, 210 mg/kg, intragastrically) on the activities of the deoxyribonucleases and the hepatic nucleic acid content was studied in female Sprague-Dawley rats. The animals were killed at various intervals after DENA treatment, and DNA, RNA, protein, DNase I-, and DNase II-activities of the liver homogenates and nuclei were assayed. Twenty-four hr after DENA administration, the RNA content and DNase I activity in the liver homogenates were diminished by about 50%; the DNA content and total DNase II activity increased by 87 and 197%, respectively. The maximum effects were observed 24 hr (RNA), 8 days (DNase I), and 8 days (DNA, DNase II) after DENA treatment. All values returned to normal within the same day (RNA), 28 days (DNase II), and 9 days (DNA, DNase I). The ratio of DNase II to DNase I activities increased in close correlation with the DNA content. In the liver nuclei, DNase II activity was increased reversibly by about 800% within a period of 2-8 days after DENA administration, whereas DNase I was not significantly affected. The results suggest that nuclear DNase II may be more specifically implicated in regulating DNA synthesis.

3696 TRANSPLACENTAL EFFECTS OF DIETHYLNITROSAMINE IN SYRIAN HAMSTERS AS RELATED TO DIFFERENT DAYS OF ADMINISTRATION DURING PREGNANCY. (Eng.) Mohr, U. (Abteilung fur Experimentelle Pathologie, Medizinische Hochschule Hannover, 3000 Hannover-Kleefeld, Karl-Wiechert-Allee 9, West Germany); Reznik-Schuller, H.; Reznik, G.; Hilfrich, J. *J. Natl. Cancer Inst.* 55(3):681-683; 1975.

The precise day or days of pregnancy on which a single dose of diethylnitrosamine (DEN) induces the highest tumor incidence in the offspring of Syrian hamsters was investigated. Female hamsters were given a single sc dose of 45 mg DEN/kg on one of the 15 days of pregnancy. In the offspring of females treated during the first 11 days of pregnancy, no respiratory tract tumors were found. The offspring of mothers given DEN during the last 4 days (12-15) of pregnancy developed respiratory tract neoplasms at a rate of up to 95%. A lower incidence of tumors in other organs seemed independent of the day of DEN treatment. It is concluded that days 12-15 of gestation are the decisive period during which the fetus is most susceptible to postnatal development of respiratory tract tumors when the mothers are exposed to DEN.

3697 *IN VITRO* METABOLISM AND MICROSOME-MEDIATED MUTAGENICITY OF DIALKYLNITROSAMINES IN RAT, HAMSTER, AND MOUSE TISSUES. (Eng.) Bartsch, H. (Int. Agency Res. Cancer, Lyon, France); Malaveille, C.; Montesano, R. *Cancer Res.* 35(3):644-651; 1975.

In an effort to understand the carcinogenic organotropism of dimethylnitrosamine (DMN) and diethylnitrosamine (DEN) in rats and hamster, the relationship between the site of metabolic conversion and the formation of mutagenic reactants was examined. Rates of conversion of $^{14}CO_2$ and/or into mutagenic reactants were measured using *Salmonella typhimurium* G-46 or TA 1530 and fortified tissue fractions *in vitro*. In general, there was a correlation between the rate of CO_2 production from DMN and DEN in tissue slices and the production of mutagenic reactants with the organ distribution of induced tumors. One exception was the hamster lung, which, while a major target organ in DEN carcinogenesis, did not convert DEN into metabolites mutagenic for *S. typhimurium* TA 1530, although the rate of CO_2 production from DEN was even higher in hamster lung slices than in liver slices. Pretreatment with phenobarbitone (1 mg/ml in drinking water for seven days) doubled the mutation frequency with DMN in liver fractions from rats, hamsters, and OF-1 mice; with DEN, the mutation frequency increased 40-fold in rats, 10-fold in mice, and 4-fold in hamster compared to untreated animals. The results support the notion that tumor localization following exposure to DMN and DEN is largely determined by the ability of the target tissue to metabolize the carcinogens.

3698 SYNCHRONIZED LIVER CELLS: A NEW TOOL FOR ANALYSIS OF CELL-CYCLE DEPENDENT CARCINOGEN-BINDING TO DNA *IN VIVO*. (Eng.) Rabes, H. M. (Pathologisches Institut der Universitat, Thalkirchner Strasse 36, D-8 Munchen 2, German Federal Republic, BRD); Iseler, G.; Tuczek, H. V.; Kerler, R. *Experientia* 31(6):686-687; 1975.

The degree of liver DNA alkylation prior to, during, and after DNA replication *in vivo* was measured in male Wistar rats subjected to two-thirds hepatectomy and injected ip with ^{14}C-labeled N,N-dimethylnitrosamine (DMNA, 0.1 μCi/g) and ^{3}H-thymidine (^{3}H-TdR, 0.8 μCi/g). In some rats, initiation of DNA synthesis in regenerating liver was blocked by a continuous infusion of hydroxyurea (HU, 1.25 x 10^{-3} M/kg/hr). These rats received ^{14}C-DMNA and ^{3}H-TdR either during the continuous HU infusion (beginning 14 hr after partial hepatectomy), four hours after the infusion (14-39 hr after partial hepatectomy), or eight hours after the infusion (47 hr after partial hepatectomy). Specific activity of DNA from ^{3}H-TdR was low in the presynthetic G_1 phase of the cell cycle and during the HU-induced inhibition of DNA synthesis at 28 hr after partial hepatectomy. DNA synthesis increased markedly four hours after release from the HU block, but declined again after another four hours. Concomitant with the upsurge in DNA synthesis at four hours after release from the HU block, incorporation of radioactivity from ^{14}C-DMNA increased significantly. The specific activity of DNA from ^{14}C-DMNA did not decline after the decline of DNA synthesis at eight hours after the HU block. These results indicate that the uptake of ^{14}C radioactivity from the labeled methyl groups in DMNA is low in G_1 phase, enhanced in G_2 phase, and highest in the S phase. The site, degree, and persistence of possible alkylation in specific carcinogen-binding to DNA remains to be evaluated.

3699 MUTAGENICITY OF DIMETHYLNITROSAMINE TO MAMMALIAN CELLS AS DETERMINED BY THE USE OF MOUSE LIVER MICROSOMES. (Eng.) Umeda, M. (Yokohama City Univ. Sch. Medicine, Urafune-cho, Minami-ku, Yokohama 232, Japan); Saito, M. *Mutat. Res.* 30(2):249-254; 1975.

The mutagenicity of dimethylnitrosamine (DMN) to mammalian cells was investigated using a metabolic activation system. 8-Azaguanine (8-AG)-sensitive FM3A cells derived from a C3H mouse mammary carcinoma were incubated with DMN (225μM), NADPH (2.5-18μM) and a microsomal suspension prepared from the livers of 8-12-wk-old male DDD mice. The treated cells were overlayed on agarose plates with or without 20 μg/ml of 8 AG. After 12-14 days, the colonies were counted. DMN alone caused little change in the mutation frequency of the FM3A cells over control values. However, when the cells were incubated with DMN plus NADPH and the microsomal solution, the mutation frequency was increased 7.4-4.9 times compared with controls. The mutation frequency in the complete reaction mixture increased proportionally to the incubation time up to 30 min and then leveled off. The mutation frequency was highest after incubation in complete medium for 30 min followed by a 2-day expression period in growth medium. Concentrations of NADPH greater than 0.3 mM were sufficient to support the high mutation frequency. The results show that mutagenic frequencies induced by liver microsomes from DDD and C3H mice are similar, but AKR microsomes induce a lower mutagenic frequency.

3700 DEGRADATION OF *N*-NITROSAMINES BY INTESTINAL BACTERIA. (Eng.) Rowland, I. R. (Br. Ind. Biol. Res. Assoc., Carshalton, England); Grasso, P. *Appl. Microbiol.* 29(1):7-12; 1975.

Bacteria, commonly found in the alimentary tracts of man and animals, and capable of degrading diphenylnitrosamine (DPN) and dimethylnitrosamine (DMN) were examined for their importance in reducing nitrosamine levels in man. Five main groups of bacteria were isolated from the gastrointestinal tract of male Wistar rats: Escherichia, bacteriodes, bifidobacterium, *Lactobacillus*, and Streptococcus *faecalis*. The experiments were performed at ph 7.0 in the absence of glucose. All were under anaerobic conditions, except for *E. coli* strains and *Proteus* species. The ability to degrade DPN and DMN appeared to be a common property of bacteria in most of the bacterial types tested, although the rate of nitrosamine breakdown varied considerably both within and between groups. Strains of *Lactobacilli* and *E. coli* were the most active in degrading nitrosamines. Several strains of bifidobacteria and bacteroides which constitute more than 99% of the total number of bacteria in the alimentary tracts of man and animals were able to degrade DPN and DMN, but their rates of breakdown were lower than other bacteria tested. The observation that several species could degrade DPN but not DMN suggests the two processes may be mediated by different mechanisms. In situations where small quantities of nitrosamines in ingested food come into contact with intestinal bacterial synthesis of nitrosamines is possible, it is feasible that net synthesis of nitrosamines may be reduced by the degradative action of bacterial enzymes.

3701 CARCINOGENICITY OF 4-HYDROXYBUTYL-BUTYLNITROSAMINE IN SYRIAN HAMSTERS. (Eng.) Althoff, J. (Eppley Inst. Res. Cancer, 42nd and Dewey Ave., Omaha, Nebr. 68105); Kruger, F. W. *Cancer Lett.* 1(1): 15-19; 1975.

The biological effects of chronic treatment with the dibutylnitrosamine (DBN) metabolite, 4-hydroxybutyl-butylnitrosamine (HBBN), were studied in Syrian hamsters to determine whether their response to DBN is similar to that previously reported for rats. The LD_{50} of HBBN was estimated to be 3.0 g/kg after eight days of observation of ten hamsters given sc doses of HBBN (1, 2, 4, and 8 g/kg). A positive dose-effect relationship was demonstrated after 75 wk of HBBN administration (0.6, 0.3, and 0.15 g/kg, sc, once weekly) to 90 animals. This dose-effect relationship was mainly due to the occurrence of neoplasms in the trachea, bile ducts, and urinary bladder. The occurrence of neoplasms in organs other than the urinary bladder contrasts

with results obtained previously in rats and demonstrates that HBBN is not a specific bladder carcinogen.

3702 CARCINOGENIC EFFECTS OF DI-*N*-PROPYLNITROSAMINE, β-HYDROXYPROPYL-*N*-PROPYLNITROSAMINE, AND METHYL-*N*-PROPYLNITROSAMINE ON SPRAGUE-DAWLEY RATS. (Eng.) Reznik, G. (Abteilung für Experimentelle Pathologie, Medizinische Hochschule Hannover, Karl-Wiechert-Allee 9, 3000 Hannover-Kleefeld, West Germany); Mohr, U.; Krüger, F. W. *J. Natl. Cancer Inst.* 54(4):937-943; 1975.

The reaction of 220 rats to β-hydroxypropyl-*n*-propylnitrosamine (HPPN), methyl-*n*-propylnitrosamine (MPN), and di-*n*-propylnitrosamine (DPN) was investigated to clarify whether all three substances had similar effects. Sprague-Dawley rats received either 1/5, 1/10, or 1/20 the LD50 of DPN (487.2 mg/kg), MPN (106 mg/kg) or HPPN (1,273 mg/kg) sc once weekly for life. Surviving controls were killed 100 wk after the start of the experiment. Chronic DPN treatment induced the most neoplasms in the nasal cavities (up to 70% of each group of 20) and the liver (up to 60%). Other tumors developed in the endoturbinals (up to 60%), lungs (up to 40%), esophagus (up to 50%), and kidneys (up to 30%). Chronic MPN treatment induced the most esophageal (up to 100%) and hepatic (up to 90%) neoplasms. HPPN treatment caused up to 70% of the animals to develop 23 squamous cell papillomas and 21 carcinomas of the maxilloturbinals and nasoturbinals of the maxillary sinuses. Tumors induced by HPPN treatment in the endoturbinals invaded the brain. Up to 60% of the HPPN-treated animals had hepatocellular carcinomas. The results demonstrate that, in rats, DPN and its metabolites induce neoplasms of the apical and caudal nasal cavities, esophagus and liver. An increased tumor rate is observed with decreased dosage especially in HPPN. MPN possesses the highest carcinogenicity of the three compounds tested.

3703 ACUTE BIOCHEMICAL AND MORPHOLOGICAL EFFECTS OF *N*-NITROSOMORPHOLINE IN COMPARISON TO DIETHYL- AND DIETHYLNITROSAMINE. (Eng.) Stewart, B. . (Sch. Pathology, Univ. New South Wales, Box 1 P.O. ensington 2033, N.S.W. Australia); Hicks, R. M.; agee, P. N. *Chem. Biol. Interact.* 11(5):413-429; 975.

ome of the biochemical and morphological effects of toxic dose of nitrosomorpholine on the liver of emale Wistar rats were compared with those produced diethyl- and dimethylnitrosamine. Rats were injected ip with dimethylnitrosamine, 20 mg/kg; diethylnitrosamine, 250 mg/kg; and nitrosomorpholine 00 mg/kg in 0.9% NaCl solution and killed at various times after treatment. The rates of synthesis RNA and protein *in vivo* were measured by administration of [^{14}C]orotate and [^{14}C]leucine, respectively, and by determining the acid-soluble and incorporated radioactivity. DNA-dependent RNA polymerase activity was assayed in liver nuclei isolated om rats treated with nitrosomorpholine. Total lysomes were prepared from liver 1, 2, 4, 6, 16, d 24 hr after treatment with diethylnitrosamine and nitrosomorpholine and analyzed by sucrose gradient centrifugation. Liver sections from rats killed at 0.5, 1, 2, 4, 6, 24, and 48 hr after treatment were examined by light and electron microscopy. Hepatotoxic doses of the nitrosamines caused inhibition of incorporation of [^{14}C]leucine into hepatic proteins; this was accompanied by progressive disaggregation of polysomes, which paralleled the known time course of metabolism of each compound. Dimethylnitrosamine and N-nitrosomorpholine inhibited incorporation of [^{14}C]orotate into liver RNA, but diethylnitrosamine caused a slight stimulation. Electron microscopy revealed similar hepatic cytoplasmic changes induced by each nitrosamine, including dilation and degranulation of the rough endoplasmic reticulum. Nuclear changes differed with each compound, N-nitrosomorpholine having more marked effects than either of the other two compounds. It is suggested that the differences between dimethylnitrosamine, diethylnitrosamine, and nitrosomorpholine in their effect on nuclear morphology is a consequence of differences in the initial reaction of these carcinogens with DNA. It is also suggested that the similar pattern of cytoplasmic changes induced by the three nitrosamines is a consequence of their metabolism by the liver. Their acute toxicity is probably dependent on this metabolism, and it is possible that intermediates produced from either the dialkyl or cyclic nitrosamines may be involved in the carcinogenic process.

3704 EFFECTS OF NITROSOCARBARYL ON BALB/3T3 CELLS. (Eng.) Quarles, J. M. (Univ. Tennessee--Oak Ridge Graduate Sch. Biomedical Sciences, Oak Ridge, Tenn. 37830); Tennant, R. W. *Cancer Res.* 35(10):2637-2645; 1975.

Transformation of mammalian cells in culture and activation of endogenous leukemia viruses was attempted with *N*-nitrosocarbaryl. Carbaryl (*N*-methyl-1-naphthylcarbamate) and *N*-nitrosocarbaryl were tested on BALB/3T3 (clone A31) cells in culture. Nitrosocarbaryl (10 or 20 μg/ml), but not carbaryl (10, 20, or 40 μg/ml), caused transformation of the BALB/3T3 fibroblasts, but neither induced the complete expression of endogenous murine leukemia virus. Transformed cells differed from the parental control cells by loss of contact inhibition, change in morphology, growth in soft agar, growth to higher saturation densities, and tumorigenicity in normal newborn and irradiated weanling BALB/c mice and athymic (nude) mice. Transformed clones were negative for expression of RNA tumor virus antigens, viral reverse transcriptase, and infectious virus. Thus, it appears that nitrosocarbaryl can transform BALB/3T3 cells to tumorigenic cells with altered biological properties but without complete activation of RNA tumor viruses in the transformed cells. Expression of viral antigen in the transformed cells was inducible by iododeoxyuridine, indicating that the endogenous viral genome was retained in an unexpressed state. Nitrosocarbaryl may be a weak carcinogen.

3705 TRANSFORMATION OF HUMAN CELLS IN CULTURE BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE. (Eng.) Rhim, J. S. (Microbiological Assoc., Beth-

esda, Md. 20014); Park, D. K.; Arnstein, P.; Huebner, R. J.; Weisburger, E. K.; Nelson-Rees, W. A. *Nature* 256(5520):751-753; 1975.

The possibility of using continuous lines of human sarcoma cells for chemical transformation was investigated. The human osteosarcoma clonal line was maintained in Eagle's minimal essential medium with 10% fetal calf serum until the 31st subculture, when the medium was replaced with media containing 5.0-0.01 g/ml N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in 0.5% dimethylsulfoxide. Doses of 1.0 g/ml MNNG or greater were fatal. In cultures treated with 1.0 µg/ml MNNG, morphological alterations of cells and abnormal growth patterns were noted in the sixth subculture, 55-59 days after treatment. Alterations induced by 0.01 µg/ml of the carcinogen became more pronounced after further subcultivation. The morphological changes in these cultures were similar to those previously observed in human osteosarcoma cells transformed by Kirsten sarcoma virus. Foci of transformed cells consisted mainly of randomly oriented, spindle-shaped cells with nuclear and cytoplasmic overlapping that stained heavily with Giemsa. The growth rate of the cells was double that of control cells treated with dimethyl sulfoxide alone. Chromosome analysis showed that the MNNG-transformed cells had the same markers as reported for untreated parental cells. All five NIH nude athymic mice injected sc with 5 x 10^6 cells from cultures treated with 0.01 g/ml MNNG developed poorly differentiated sarcoma within two wk of inoculation. Three of five mice given cells from cultures treated with 0.1 g/ml MNNG developed small, persisting nodules that resembled osteosarcomas. The sarcomas were progressive and transplantable. The system used in this study represents an initial advance in the direction of the *in vitro* transformation of human cells with chemical carcinogens.

3706 IMMUNOFLUORESCENT STAINING OF GASTRIC MUCOSAL GLYCOPROTEIN IN GASTRIC CARCINOMA OF DOGS AND RATS INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE. (Eng.) Kawasaki, H. (Kurume Univ. Sch. Med., 67 Asahi-machi, Kurume 830, Japan); Nakayama, K.; Kimoto, E. *Gann* 66(4):427-431; 1975.

Immunohistological studies, using the fluorescein isothiocyanate-labeled antibody against gastric mucosal glycoprotein, were made during the development of gastric cancer, induced in pointer dogs and Wistar rats by po administration of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). The dogs and rats were given 167 g/ml MNNG in their drinking water. In an early stage, the regenerative glands were lined by fluorescent mucus cells. Carcinoma cells of orderly glandular structure, produced in the dogs after 485 days, were devoid of fluorescence. Carcinoma cells of less differentiation, produced in the rats during a further advanced stage (540 days), were well fluorescent. The immunofluorescent profiles of such experimentally induced gastric carcinoma were found to be the same as those of human gastric adenocarcinoma.

3707 CARCINOGENICITY OF *N*-NITROSO-3,4-DICHLORO- AND *N*-NITROSO-3,4-DIBROMOPIPERIDINE IN RATS. (Eng.) Lijinsky, W. (Biology Div., Oak Ridge Natl. Lab., Oak Ridge, Tenn. 37830); Taylor, H. W. *Cancer Res.* 35(11/Part 1):3209-3211; 1975.

Comparative carcinogenic activity of nitrosopiperidine, and two of its halogenated derivatives, 3,4-dichloro- and 3,4-dibromonitrosopiperidine, was studied in male Sprague-Dawley rats. Using distilled water and alcohol as solvents, equimolar concentrations (0.35 mM) or 3,4-dichloro- and 3,4-dibromonitrosopiperidine and a higher concentration (0.88 mM) of nitrosopiperidine were administered po to groups of 15 rats. Each group received 60 ml of a solution containing one of the compounds daily five days a week; tap water was given on the other two days. When rats in a group began to die, dosing was discontinued. Animals were kept until they died naturally, or they were killed when moribund. Necropsies were then performed, and organs with tumors or lesions were fixed for histological examination. Administration of the dichloro compound (total dose 0.5 mM) for 15 wk caused death of all 15 rats at 24 wk; 27 wk of the dibromo compound (total dose 1.0 mM) caused the death of 15 rats at 41 wk. Animals died of tumors of the tongue, esophagus, stomach, and respiratory system. After the three-fold higher daily dose of nitrosopiperidine (total dose 3.9 mM), 8 of 15 rats were still alive at 40 wk. Not until 55 wk were all in this group dead of tumors similar to those induced by the halogenated piperidines except for absence of respiratory system tumors. Whereas substitution of bromine in the position β to the nitroso function of nitrosopiperidine increases carcinogenicity to a lesser extent than substitution of chlorine, both derivatives are far more active than the parent compound.

3708 SPECIFIC UPTAKE OF LABELED N-NITROSOMETHYLUREA IN THE PANCREATIC ISLETS OF CHINESE HAMSTERS. (Eng.) Tjalve, H. (Dept. Toxicology and Dept. Pathology, Univ. Uppsala, Box 573, S-751 23 Uppsala, Sweden); Wilander, E. *Experientia* 31(9):1061-1062; 1975.

The distribution of labeled N-nitrosomethylurea (NMU) was studied by whole-body autoradiography in mice and Chinese hamsters. In hamsters injected (40 mg/kg, iv) with labeled NMU, a selective uptake of radioactivity occurred in the pancreatic islets after 30 min. At the 1 hr survival interval, the radioactivity in the pancreatic islets and in the liver was the highest in the body. Later the radioactivity in the pancreatic islets decreased and did not exceed that in the exocrine pancreas or in the blood. The radioactivity in the pancreatic islets of the mice (C57-Bl) was low and did not exceed the level of the blood. The accumulated isotope may be a metabolite of NMU in the Chinese hamsters. Previous work showed that pancreatic islet β-cell destruction in mice has been obtained only with high doses of NMU (230 mg/kg). In Chinese hamsters, doses of 50 mg/kg of NMU resulted in diabetes. It appears that the diabetogenic property of NMU is related to the selective accumulation of NMU or its metabolites in the pancreatic islets.

3709 THE INFLUENCE OF DIETARY NITRATE ON NITRATE CONCENTRATION IN EGG YOLK AND ALBUMEN. (Eng.) Lee, H. W. (Dept. Dairy and Poultry Science, Kansas State Univ., Manhattan, Kansas 66506); Adams, A. W.; Cunningham, F. E. *Poult. Sci.* 54(2):475-478; 1975.

The influence of nitrate, administered at various levels to laying hens, on nitrate composition of eggs was determined. Sodium nitrate (0-2,000 ppm) was added to the drinking water of 32-wk-old S.C. White Leghorn pullets. Eggs collected once a week for eight weeks were analyzed for nitrate content using a cadmium column for the reduction of nitrate and subsequent analysis of nitrite by azo dye formation in acidic media by diazotization and coupling with 1-naphthylamine. Increasing levels of nitrate in the drinking water resulted in increasing levels of nitrate in albumen and yolk. Higher levels of nitrate were found in the yolk than in the albumen. When birds were started on the experiment, nitrate in the drinking water was reflected by immediate increases in nitrate content of the eggs. The nitrate content of eggs from birds receiving 1,000 ppm $NaNO_3$ (728 ppm NO_3^-) exceeded the 45 ppm permissible level of nitrate in drinking water for human beings.

3710 INHIBITION OF DNA REPLICATIVE SYNTHESIS AND DNA REPAIR SYNTHESIS IN HUMAN AND MOUSE CELLS IN CULTURE BY CIGARETTE SMOKE CONDENSATE FRACTIONS. (Eng.) Rasmussen, R. E. (Coll. Medicine, Univ. California, Irvine, CA. 92664). *Life Sci.* 17(5):767-774; 1975.

Twelve cigarette smoke condensate fractions were tested for their ability to inhibit replicative DNA synthesis and DNA excision repair synthesis in cultures of human fibroblasts and Swiss mouse embryo cells. Replicative DNA synthesis was measured in cultures allowed to grow until confluent in a humidified atmosphere with 5% CO_2 at 37 C, and then incubated for two hours in medium containing a smoke condensate fraction and ^{3}H-thymidine. DNA repair synthesis was measured in cultures irradiated with UV light (20 joules/m^2, 1 joules/m^2/sec) prior to incubation in medium containing ^{3}H-thymidine and the smoke condensate fractions, and also with 10^{-2}M hydroxyurea which suppressed replicative DNA synthesis. None of the fractions showed any specificity for the inhibition of DNA repair and, in general, repair synthesis was less sensitive to inhibition than was replicative synthesis. In most cases, DNA synthesis in the human cells was more sensitive to inhibition than that in the mouse cells. The inhibitory activity of the fractions was compared with data on their tumor-promoting or cell-transforming activity and their ability to induce aryl hydrocarbon hydroxylase activity *in vivo*. The four fractions reported as having tumor-promoting activity were somewhat inhibitory to both replicative and repair DNA synthesis; however, three fractions without tumor-promoting activity were also inhibitors. The correlation of DNA synthesis inhibition with other biological activities was incomplete, although the single most inhibitory fraction is active in other bioassays. The specific compounds in the condensate fractions which are responsible for their activity have not been identified.

3711 INHALATION EXPERIMENTS WITH ^{14}C-LABELED CIGARETTE SMOKE. II. THE DISTRIBUTION OF CIGARETTE SMOKE PARTICLES IN THE HAMSTER RESPIRATORY TRACT AFTER EXPOSURE IN TWO DIFFERENT SMOKING SYSTEMS. (Eng.) Kmoch, N. (Medizinische Hochschule Hannover, 3000 Hannover-Kleefeld, Karl-Wiechert-Allee 9, W. Germany); Reznik, G.; Mohr, U. *Toxicology* 4(3):373-383; 1975.

Thirty-two male and 37 female Syrian golden hamsters were exposed to the smoke of [^{14}C]dotriacontane-16,17 ([^{14}C]DOT)-labeled cigarettes in two different exposure systems differing in terms of the smoke concentration drawn into the exposure chamber. To compare the effectiveness of the two systems, the inhaled dose of ^{14}C-labeled cigarette smoke was determined in the different parts of the hamster respiratory tract. About six times more smoke particles were deposited in the respiratory tract after exposure to high smoke concentration with intermittent puffs of fresh air (closed system) than after exposure to smoke diluted with air (open system). About 80% of the diluted smoke reached the bronchi and lung compared to approximately 60% of the concentrated smoke. The remainder of the dose was trapped in the upper respiratory tract, primarily in the nose and larynx. In the open system the total dose of inhaled smoke was dependent upon the position in the exposure chamber. The higher activity recovered from the hamsters in the closed system is possibly due to the higher concentration of smoke in the exposure chamber of the closed system. The results show that the open system can increase the inhaled dose to about six times that of the closed system.

3712 SUPPRESSION OF LYMPHOCYTE FUNCTION BY PRODUCTS DERIVED FROM CIGARETTE SMOKE. (Eng.) Roszman, T. L. (Coll. Med., Univ. Kentucky, Lexington); Elliott, L. H.; Rogers, A. S. *Am. Rev. Respir. Dis.* 111(4):453-457; 1975.

The effects of various concentrations of nicotine and a water soluble fraction (WSF) from whole cigarette smoke on the transformation of rabbit peripheral lymphocytes stimulated by concanavalin A (Con A) or goat anti-rabbit Fab were determined. New Zealand adult female rabbits were used. After exposure to [H^3]-thymidine for 16 hr, lymphocytes stimulated with optimal doses of the mitogens showed an inhibition of [H^3]-thymidine incorporation into the DNA. The concentration of nicotine required to reduce the Con A and anti-Fab responses to 50% of control levels was 120 μg/ml and 90 μg/ml, respectively. About 48 μg/ml WSF was required to suppress DNA synthesis of cultures stimulated with Con A to 50% of control values, and 27 μg/ml for cultures stimulated with anti-Fab. Because cell viabilities of cultures exposed to various concentrations of nicotine or WSF were essentially the same as the viability of unexposed cultures, mitogen suppression could not be attributed to cytotoxicity. Neither nicotine nor WSF were mi-

togenic by themselves. Because previous studies have indicated that Con A specifically stimulates rabbit T-cells, whereas anti-Fab is specific for B-cells, this study indicates that both cell functions are susceptible to the action of nicotine and WSF. The authors conclude that *in vitro* systems can be used in investigating mechanisms involved in the effects of cigarette smoke on the immune response.

3713 ACTION OF SULPIRIDE ON SPONTANEOUS DEVELOPMENT OF BREAST CANCER IN MICE. (Fre.) Rudali, G. (Lab. Genet., Curie Foundation, Inst. Radium, Paris, France); Aussepe, L. *C. R. Acad. Sci. Paris Ser. D* 280:1209-1211; 1975.

The effect of sulpiride on the incidence of spontaneous mammary tumors in male and female (C3H x RIII)F_1 mice subjected to castration and/or adrenalectomy was observed. Sulpiride stimulates lactation, probably by inducing the release of prolactin. Beginning at 30 days of age, sulpiride was administered (120 µg, po) until the mice died or were killed *in extremis*. Mice were examined weekly for the appearance of tumors. Castrated, adrenalectomized females had a much lower incidence of tumors (14%) compared to intact females (91.5%). However, sulpiride did not increase the incidence. Compared to untreated mice, sulpiride did not alter the incidence of mammary tumors in castrated males or females. Histological examination of female mice on sulpiride revealed mammary development and milk in the acini and ducts. An increase in the number of carmine-stained cells in the pituitary was also observed. It is concluded that a chemical compound that stimulates secretion of prolactin may not necessarily be carcinogenic for the mammary gland.

3714 NEOPLASTIC AND LIFE-SPAN EFFECTS OF CHRONIC EXPOSURE TO TRITIUM. I. EFFECTS ON ADULT RATS EXPOSED DURING PREGNANCY. (Eng.) Cahill, D. F. (Natl. Environmental Res. Center, Research Triangle Park, N.C. 27711); Wright, J. F.; Godbold, J. H.; Ward, J. M.; Laskey, J. W.; Tompkins, E. A. *J. Natl. Cancer Inst.* 55(2):371-374; 1975.

Observations were made on the late effects of irradiation during pregnancy in order to determine how changes in hormone patterns may influence the neoplastic potential or irradiation on mammary tissue. One hundred and nine pregnant female Sprague-Dawley rats were inoculated ip with tritiated water (HTO), and equilibrium levels were maintained throughout pregnancy by HTO in drinking water. The tritium activities were 1, 10, 50, and 100 µCi HTO/ml body water, which provided cumulative, whole-body radiation doses of approximately 6.6, 66, 330, and 660 rads. Administration of the radioisotope was terminated at parturition. Throughout their life-spans and at autopsy, the dams showed an increased incidence of mammary fibroadenomas at exposure to 330 and 660 rads. Although the data for the incidence of malignant mammary neoplasms were consistent with a linear dose response, the small numbers of tumors preclude specific definition of the dose-response curve. Postexposure life-spans for dams chronically exposed to 66, 330, and 660 rads during pregnancy were reduced by 14, 24, and 22%, respectively. Accelerated aging was also demonstrated in these rats: The mean age for mammary fibroadenoma onset decreased with an increasing dose of radiation. A more comprehensive investigation of the radiosensitivity of pregnant animals in advisable.

3715 EFFECTS OF THE CARCINOGEN URETHANE ON NUCLEAR RNA POLYMERASE ACTIVITIES. (Eng.) Eker, P. (The Norwegian Radium Hosp., Montebello, Oslo 3, Norway). *Eur. J. Cancer* 11(7):493-497; 1975.

The effect of urethane on RNA polymerase activity of nuclei isolated from liver and lung of male Wistar rats was investigated. The effect of the carcinogen on *in vitro* RNA synthesis with *Escherichia coli* RNA polymerase was also studied. Intraperitoneal injection of 1 mg/g urethane inhibited the Mg^{2+} -dependent RNA polymerase activity of isolated lung nuclei by about 50%. The inhibition was maximal one hour after the injection. Twenty hours after administration, the Mg^{2+}-stimulated activity was again normal. The template activity of chromatin isolated from lung nuclei was measured using *E. coli* RNA; this showed that the normal chromatin and the chromatin from urethane-treated rats was identical. The activity of Mn^{2+} plus $(NH_4)_2SO_4$-dependent RNA polymerase activity of isolated lung nuclei was not affected by urethane injection. The two RNA polymerase activities of liver nuclei were not inhibited by the carcinogen. Mg^{2+}-stimulated nuclear RNA synthesis *in vitro* was inhibited markedly by urethane at concentrations above 50 mM, whereas the Mn^{2+} plus $(NH_4)_2SO_4$-dependent activity was only slightly affected. *In vitro* RNA synthesis catalyzed by *E. coli* RNA polymerase was also inhibited by high concentrations of the carcinogen.

3716 A GAS-CHROMATOGRAPHIC METHOD FOR THE PREPARATION OF ^{14}C-LABELED VINYL CHLORIDE. (Eng.) Wagner, E. R. (Dow Chemical Co., Midland, Mich. 48640); Muelder, W. M.; Watanabe, P. G.; Hefner, R. E., Jr.; Braun, W. H.; Gehring, P. J. *J. Labelled Compd.* 11(4):535-542; 1975.

A method for producing vinyl-$^{14}C_2$ chloride (^{14}C-VC) by the dehydrohalogenation of 1,2-dichlorethane-$^{14}C_2$ (^{14}C-DCE) is described. ^{14}C-VC is produced as a gas mixed with helium by passing ^{14}C-DCE over a carbon catalyst at high temperatures. A modified Hewlett-Packard model 5750 gas chromatographic column is used. The large separation coil (2.4 m x 3 mm) is packed with 80-90 mesh Dow Corning 410 Gum on Chromosorb W (acid washed). The smaller pyrolysis tube (90 cm x 3 mm) is packed with a charcoal mixture of 20 g Chromosorb W and 10 g Darco G-60 charcoal powder. An external thermocouple allows independent heating of this portion of the column. The tube is connected to a thermal conductivity detector with a collecting syringe at the terminal end. The catalyst is heated to 470-480 C, and up to 10 µl of liquid

^{4}C-DCE (3.4 mCi/mM) is injected into the tube; ^{4}C-VC is collected in 1 ml aliquots. The efflu- nt gas is bubbled into scintillation vials of onciflour, 2-methoxyethanol and toluene (1:1.8:11) n order to measure specific activity of the syn- hesized gas. With a gas flow of about 30 ml of e/min, the thermal conductivity detector revealed our peaks of activity. Analysis by infra-red pectrometry identified the peaks as impurities, Cl, ^{14}C-VC, and unreacted ^{14}C-DCE. Gross conta- ination is avoided since the gaseous products xit at distinct intervals with little mixing. urther analyses by the gas chromatography and ass spectrometry showed that a minimum value of 6% (expressed on a mole basis) ^{14}C-VC with a spe- ific activity of 2.6 Ci/mM is generated from 5.5 l ^{14}C-DCE. The level of radioactivity of the ^{4}C-VC declined over time (50% in nine hours). he polymerization of the gas on the walls of the ollecting syringe is thought to be responsible or this. The mass spectrum of the synthesized ^{4}C-CV was identical with that of the VC standard. his procedure yields a product with 96-97% purity. he amount of ^{14}C-VC produced was limited by the mount of ^{14}C-DCE, temperature, and He flow rate.

717 THE MICRONUCLEUS TEST AS A SIMPLE MODEL, *IN VIVO*, FOR THE EVALUATION OF DRUG- NDUCED CHROMOSOME ABERRATIONS: COMPARATIVE STUDIES ITH 13 COMPOUNDS [abstract]. (Eng.) Matter, B. E. Biol. Med. Res. Div., Sandoz Ltd., Basle, Switzer- and); Grauwiler, J. *Mutat. Res.* 29(2):198-199; 975.

718 IDENTIFICATION OF *IN VITRO* CHEMICAL CAR- CINOGEN INDUCED NEOPLASTIC TRANSFORMATION F MAMMALIAN CELLS BY NONIMMUNE LEUKOCYTES [abstract]. Eng.) Evans, C. H. (Natl. Cancer Inst., Bethesda, d. 20014); DiPaolo, J. A. *Proc. Am. Assoc. Cancer es.* 16:64; 1975.

719 AFLATOXIN-INDUCED CHANGES IN HUMAN HEPATO- CYTES IN ORGAN CULTURE [abstract]. (Eng.) oyes, W. F. (Roswell Park Memorial Inst., Buffalo, .Y. 14203). *Proc. Am. Assoc. Cancer Res.* 16:26; 975.

720 MALIGNANT TRANSFORMATION WITH ARA-C, FUDR, MTX, AND BLEOMYCIN IN 10T½CL8 CELLS [ab- tract]. (Eng.) Benedict, W. F. (Children's Hosp. os Angeles, Los Angeles, Calif. 90027); Baker, M. ; Gardner, A. *Proc. Am. Assoc. Cancer Res.* 16:40; 975.

721 NON-SPECIFIC INHIBITION OF DNA REPAIR SYN- THESIS BY TUMOR PROMOTERS [abstract]. Eng.) Poirier, M. C. (Natl. Cancer Inst., Bethesda, d. 20014); Lieberman, M. W. *Proc. Am. Assoc. Can- er Res.* 16:43; 1975.

3722 STUDIES ON HIGH SUSCEPTIBILITY OF NURSING MOTHER MICE IN 2,7-FAA HEPATOCARCINOGENESIS [abstract]. (Jpn.) Kimura, I. (Aichi Cancer Center Res. Inst., Nagoya, Japan); Miyake, T., Furukawa, E.; Nishio, O. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 18.

3723 THE RELATIONSHIP OF EPIDERMAL HISTADASE LEVELS TO TUMOR PROMOTION, HYPERPLASIA AND NEOPLASIA [abstract]. (Eng.) Colburn, N. H. (Dept. Dermatology, Univ. Michigan, Ann Arbor, Mich. 48104); Head, R. A.; Lau, S. *Proc. Am. Assoc. Cancer Res.* 16:46; 1975.

3724 RAPID FORMATION OF IMINODIACETATE FROM PHOTOCHEMICAL DEGRADATION OF Fe(III)NI- TRILOTRIACETATE SOLUTIONS. (Eng.) Stolzberg, R. J. (The New England Aquarium, Boston, Mass.): Hume, D. N. *Environ. Sci. Technol.* 9(7):654-656; 1975.

3725 PHORBOLOL MYRISTATE ACETATE: A NEW META- BOLITE OF PHORBOL MYRISTATE ACETATE IN MOUSE SKIN [abstract]. (Eng.) Segal, A. (New York Univ. Medical Center, New York, N.Y. 10016); Van Duuren, B. L.; Mate, U. *Proc. Am. Assoc. Cancer Res.* 16:21; 1975.

3726 THE INTERACTION OF PHORBOL MYRISTATE ACE- TATE, A TUMOR PROMOTER, WITH RAT LIVER PLASMA MEMBRANES: A FLUORESCENCE STUDY [abstract]. (Eng.) Witz, G. (New York Univ. Medical Center, New York, N.Y. 10016); Van Duuren, B. L.; Banerjee, S. *Proc. Am. Assoc. Cancer Res.* 16:30; 1975.

3727 REDUCTION OF LEAD ACETATE TERATOGENICITY IN THE CHICK BY ASCORBIC ACID [abstract]. (Eng.) King, D. W. (Dept. Zool., Natl. Taiwan Univ., Taipei); Liu, J. *Fed. Proc.* 34(3):1049; 1975.

3728 ANALYTICAL STUDY ON THE ROLE OF POLY- CHLORINATED BIPHENYLS (PCBs) IN THE MECHANISM OF AZO DYE HEPATOCARCINOGENESIS IN RATS [abstract]. (Jpn.) Kimura, N. (Cancer Res. Inst., Kyushu Univ., Fukuoka, Japan); Kanematsu, T.; Baba, T. *Proc. Jpn. Cancer Assoc. 34th Annual Meeting, October 1975.* p. 17.

3729 THE EFFECT OF THE POTENT MUTAGEN AZIDE ON DEOXYRIBONUCLEIC ACID [abstract]. (Eng.) Sideris, E. G. (Bio. Div., Nucl. Res. Cent. Democritos, Athens, Greece); Argyrakis, M. *Mutat. Res.* 29(2): 239; 1975.

3730 BIOCHEMICAL AND HISTOCHEMICAL STUDY OF THE λ-GLUTAMYL TRANSPEPTIDASE ACTIVITY IN RAT LIVER DURING 3'-Me-DAB CARCINOGENESIS [abstract]. (Jpn.) Chisaka, N. (Sapporo Medical Coll., Sapporo, Japan); Kaneko, A.; Yoshida, Y.; Yokoyama, S.; Dempp, K.; Onoe, T. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 17.

3731 INDUCTION OF HEPATOMA AND HYPERPLASIA OF THE URINARY BLADDER IN FEMALE MICE BY FEEDING BENZIDINE DYES [abstract]. (Jpn.) Miyakawa, M. (Sch. Medicine, Kyoto Univ. Kyoto, Japan); Yoshida, O. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 17.

3732 PROTECTIVE EFFECT OF REDUCDYN AGAINST THE CHROMOSOME DAMAGING ACTIVITY OF 2,3,5-TRIETHYLENEIMINO-BENZOQUINONE-1,4 ON HUMAN LYMPHOCYTES *IN VITRO*. (Eng.) Stosiek, M. (Institut fur Humangenetik und Anthropologie der Universitat Erlangen-Nurnberg, Erlangen, West Germany); Gebhart, E. *Mutat. Res.* 29(2):284; 1975.

3733 INFLUENCE OF CROTON OIL IN HAMSTER LUNG CARCINOGENESIS [abstract]. (Eng.) Sellakumar, A. R. (New York Univ. Medical Center, New York, N.Y. 10016); Kuschner, M.; Laskin, S. *Proc. Am. Assoc. Cancer Res.* 16:57; 1975.

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3735 MICROSOMAL MEMBRANE ALTERATIONS AFTER ACUTE AND CHRONIC ETHIONINE ADMINISTRATION [abstract]. (Eng.) Kisilevsky, R. (Queen's Univ., Kingston, Canada); Weiler, L. *Fed. Proc.* 34(3):872; 1975.

3736 SCANNING ELECTRON MICROSCOPY (SEM) OBSERVATIONS OF URINARY CYTOLOGY FROM RATS FED N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL] FORMAMIDE (FANFT) [abstract]. (Eng.) Jacobs, J. (St. Vincent Hosp., Worcester, Mass. 01610); Cohen, S. M.; Arai, M.; Friedell, G. H. *Proc. Am. Assoc. Cancer Res.* 16:49; 1975.

3737 CARCINOGENICITY OF THE ANTINEOPLASTIC AGENT 4(5)-(3,3-DI-METHYL-1-TRIAZENO) IMIDAZOLE-5(4)-CARBOXAMIDE (NSC-45388, DTIC) IN GERMFREE RATS [abstract]. (Eng.) Croft, W. A., Jr. (Univ. Wisconsin Medical Sch., Madison); Skibba, J. L.; Bryan, G. T. *Fed. Proc.* 34(3):229; 1975.

3738 MECHANISM OF ACTION OF STEROIDAL ANTI-INFLAMMATORY AGENTS THAT INHIBIT SKIN CARCINOGENESIS [abstract]. (Eng.) Slaga, T. J. (Fred Hutchinson Cancer Res. Center, Seattle, Wash. 98104); Thompson, S.; Schwarz, J. A. *Proc. Am. Assoc. Cancer Res.* 16:37; 1975.

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3740 INFLUENCE OF ANTI-OESTROGENS ON THE SPECIFIC BINDING *IN VITRO* OF [^{3}H]OESTRADIOL BY CYTOSOL OF RAT MAMMARY TUMOURS AND HUMAN BREAST CARCINOMATA. (Eng.) Powell-Jones, W. (Welsh Natl. Sch. of Medicine, Health Park, Cardiff CF4 4XX, U.K.); Jenner, D. A.; Blamey, R. W.; Davies, P.; Griffiths, K. *Biochem. J.* 150(1):71-75; 1975.

3741 PROLACTIN AND ESTRADIOL CONTROL GROWTH OF RAT MAMMARY ADENOCARCINOMA CELLS *IN VITRO* [abstract]. (Eng.) Chan, P.-C. (American Health Foundation, Valhalla, N.Y. 10595); Cohen, L. A.; Wynder, E. L. *Proc. Am. Assoc. Cancer Res.* 16:40; 1975.

3742 COMPARISON OF CYTOCHROME P450 AND ARYL HYDROCARBON HYDROXYLASE LEVELS WITH BINDING OF AROMATIC HYDROCARBONS TO DNA IN UNINDUCED AND INDUCED RAT LIVER NUCLEI [abstract]. (Eng.) Rogan, E. G. (Eppley Inst. for Res. in Cancer, Univ. Nebraska, Omaha, Nebr. 68105); Cavalieri, E. *Proc. Am. Assoc. Cancer Res.* 16:60; 1975.

3743 INHIBITION OF ENZYME-CATALYZED, IRREVERSIBLE BINDING OF BENZO(α)-PYRENE BY MOUSE LUNG MICROSOMES [abstract]. (Eng.) Shih, T.-W. (Southern Res. Inst., Birmingham, Ala. 35205). *Proc. Am. Assoc. Cancer Res.* 16:25; 1975.

3744 BINDING OF LIGHT-EXPOSED BENZ(a)ANTHRACENE (BA) DERIVATIVES TO GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE (GPDH) AND MAMMARY TISSUE [abstract]. (Eng.) Grubbs, C. J. (Univ. Tennessee Center Health Sciences, Memphis, Tenn. 38163); Wood, J. L. *Proc. Am. Assoc. Cancer Res.* 16:16; 1975.

3745 HISTOCHEMICAL-DEMONSTRATION OF POLYNUCLEOTIDE PHOSPHORYLASE SYNTHETIC ACTIVITY IN RAT AND HUMAN MAMMARY CARCINOMA [abstract]. (Eng.) Tsou, K. C. (Univ. Pennsylvania Sch. Medicine, Philadelphia, Pa. 19174); Yip, K. F.; Lo, K. W.; Levin, J. M.; Rhoads, J. E.; Rosato, F. E.; Ruberg, R.; Randall, P. *Proc. Am. Assoc. Cancer Res.* 16:26; 1975.

3746 THE EFFECT OF ISOPROPYLVALERAMIDE (IVA) AND ALLYLISOPROPYLACETAMIDE (AIA) ON CARCINOGEN-INDUCED DEPRESSION OF DNA SYNTHESIS *IN VIVO* AND CYTOTOXICITY AND MALIGNANT TRANSFORMATION *IN VITRO* [abstract]. (Eng.) Langenbach. R. (Univ. Nebraska Medical Center, Omaha, Nebr. 68105); Somogyi, A. *Proc. Am. Assoc. Cancer Res.* 16:41; 1975.

3747 BINDING OF DIMETHYLBENZANTHRACINE (DMBA) TO ESTROGEN RECEPTOR PROTEIN IN RAT UTERI AND MAMMARY GLANDS [abstract]. (Eng.) Lucid, S. W. (Univ. Oklahoma Health Sciences Center, Oklahoma City, Okla. 73104); Shaw, M. T. *Proc. Am. Assoc. Cancer Res.* 16:50; 1975.

3748 TRANSFORMATION OF MOUSE FIBROBLASTS BY 8,9-DIHYDRODIOLS OF 7-METHYLBENZ(A)ANTHRACENE AND 7,12-DIMETHYLBENZ(A)ANTHRACENE [abstract]. (Eng.) Marquardt, H. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021); Grover, P. L.; Sims, P. *Proc. Am. Assoc. Cancer Res.* 16:17; 1975.

3749 EFFECT OF CARCINOGENS ON ATHEROSCLEROSIS IN THE CHICKEN AORTA [abstract]. (Eng.) Albert, R. E. (New York Univ. Medical Center, New York, N.Y. 10016); Nishizumi, M.; Burns, F. *Proc. Am. Assoc. Cancer Res.* 16:25; 1975.

3750 PRODUCTS OBTAINED AFTER *IN VITRO* REACTION OF 7,12-DIMETHYLBENZ[*a*]ANTHRACENE 5,6-OXIDE WITH NUCLEIC ACIDS. (Eng.) Blobstein, S. H. (Columbia Univ. Coll. Physicians Surg., New York, N.Y.); Weinstein, I. B.; Grunberger, D.; Weisgras, J.; Harvey, R. G. *Biochemistry* 14(15):3451-3458; 1975.

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3752 EFFECT OF LEUPEPTIN ON CARCINOGENESIS OF RAT MAMMARY TUMOR INDUCED BY 7,12,-DMBA [abstract]. (Jpn.) Fukui, Y. (Kansai Medical Univ., Osaka Japan): Takamura, C.; Yamamura, M.; Yamamoto, M. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 20.

3753 HISTOPATHOLOGIC OBSERVATIONS ON MAMMARY TUMORS IN SPRAGUE-DAWLEY FEMALE RATS [abstract]. (Jpn.) Morii, S. (Kansai Medical Univ., Moriguchi, Japan); Izumi, H.; Fujii, T.; Kitajima, T.; Murakami, Y. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 20.

3754 DMBA-INDUCED STEM-CELL LEUKEMOGENESIS: INFLUENCE OF PITUITARY PROLACTIN [abstract]. (Eng.) Welsch, C. W. (Dept. Anat., Michigan State Univ., East Lansing, Mich.); Horwitz, J.; Huggins, C. B. *Proc. Am. Assoc. Cancer Res.* 16:30; 1975.

3755 EFFECT OF CARCINOGEN ON PITUITARY PROLACTIN RELEASE AND SYNTHESIS [abstract]. (Eng.) Chao, T. L. (Roswell Park Memorial Inst., 666 Elm Street, Buffalo, N.Y. 14203); Sinha, D. *Proc. Am. Assoc. Cancer Res.* 16:28; 1975.

3756 3-METHYLCHOLANTHRENE (MC) ADMINISTRATION AND THE FORMATION OF POLY A-CONTAINING RNA IN RAT LIVER [abstract]. (Eng.) Lanclos, K. D. (Medical Coll. Georgia, Augusta, Ga. 30902); Bresnick, E. *Proc. Am. Assoc. Cancer Res.* 16:61; 1975.

3757 CHROMOSOME ANALYSIS OF BONE MARROW AND NUCLEUS ANOMALY TEST IN MAMMALS AFTER TREATMENT WITH INH [abstract]. (Eng.) Muller, D. (No affiliation); Grafe, A.; Miltenburger, H. G.; Rohrborn, G.; Schulze-Schenking, M. *Mutat. Res.* 29(2):256-257; 1975.

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3759 THE EFFECT OF CYTOSINE ARABINOSIDE ON METHYL METHANESULFONATE INDUCED DNA "REPAIR" [abstract]. (Eng.) Bottomley, R. (Oklahoma Medical Res. Foundation, Oklahoma City, Okla. 73104); Garner, W.; Hawrylko, J. *Proc. Am. Assoc. Cancer Res.* 16:53; 1975.

3760 COLLABORATIVE STUDY OF MMS MUTAGENICITY WITH THE DOMINANT LETHAL ASSAY IN MICE [abstract]. (Eng.) Ehling, U. H. (Gesellschaft fur Strahlen- und Umweltforschung, Neuherberg); Frohberg, H.; Schulze-Schencking, M.; Merck, E.; Lang, R.; Lorke, D.; Machemer, L.; Matter, B. E.; Muller, D.; Rohrborn, G.; Buselmaier, W. *Mutat. Res.* 29(2):261; 1975.

3761 EXPERIMENTAL ISLET-CELL ADENOMA OF THE PANCREAS IN RATS BY MONOCROTALINE [abstract]. (Jpn.) Hayashi, Y. (Shionogi Res. Lab., Osaka, Japan); Hasegawa, T.; Imai, K.; Katayama, H. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 19.

3762 A POLAROGRAPHIC AND SPECTRAL STUDY OF SOME C- AND N-NITROSO COMPOUNDS. (Eng.) Smyth, W. F. (Chem. Dept., Chelsea Coll., London, England); Watkiss, P.; Burmicz, J. S.; Hanley, H. O. *Anal. Chim. Acta* 78(1):81-92; 1975.

3763 HISTOGENESIS OF LIVER CANCER IN MEDAKAS (*ORYZIAS LATIPES*) BY DIETHYLNITROSAMINE (DENA) [abstract]. (Jpn.) Ishikawa, T. (Cancer Inst., Tokyo, Japan); Takayama, S. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 16.

3764 DIAGNOSIS OF EXPERIMENTALLY INDUCED BRONCHOGENIC TUMOURS IN THE EUROPEAN HAMSTER WITH BRONCHOGRAPHS. (Eng.) Eckel, H. (Med. Hochschule Hannover Abt. f. experimentelle Pathologie D-3000 Hannover-Kleefeld Karl-Weichert-Allee 9 West Germany); Reznik-Schuller, H.; Reznik, G.; Ohse, G.; Mohr, U. *Z. Krebsforsch.* 83(3):207-212; 1975.

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3767 EXPERIMENTAL STUDIES ON CARCINOGENICITY OF QUINOLINE AND 2-CHLOROQUINOLINE [abstract]. (Jpn.) Hirao, K. (1st Dept. Pathology, Nagoya City Univ., Nagoya, Japan); Shinohara, Y.; Hananouchi, M.; Ogiso, T.; Kawabata, H.; Takahashi, M.; Ito, N. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 17.

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3769 INHIBITION OF DNA SYNTHESIS AND DNA REPAIR BY TOBACCO SMOKE CONDENSATE FRACTIONS AND OTHER TUMOR PROMOTERS [abstract]. (Eng.) Rasmussen, R. E. (Univ. California, San Francisco, Calif. 94143). *Proc. Am. Assoc. Cancer Res.* 16:60; 1975.

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See also:

* (Rev): 3602, 3603, 3604, 3605, 3606, 3607, 3608, 3609, 3610, 3618, 3623, 3627, 3629, 3630, 3635, 3636, 3637, 3638, 3639, 3640, 3641, 3642, 3643, 3660, 3661, 3662, 3663, 3664, 3665
* (Phys): 3778
* (Viral): 3870
* (Immun): 3896, 3939, 3945, 3956, 3959
* (Path): 4024, 4036, 4077, 4096, 4097, 4098, 4099
* (Epid-Biom): 4116, 4121, 4124, 4125, 4126, 4127, 4128, 4135, 4136, 4137, 4138, 4141

3771 ACUTE MYELOGENOUS LEUKEMIA FOLLOWING FALLOUT RADIATION EXPOSURE. (Eng.)
Conard, R. A. (Brookhaven Natl. Lab., Upton, N.Y. 11973). *J.A.M.A.* 232(13):1356-1357; 1975.

A case history is presented of a 19-yr-old Marshallese man, who had been exposed to radioactive fallout at the age of 1 yr. During the first 2 days following exposure, the patient experienced nausea, vomiting, and itching of the skin. By 2 wk, transient beta-ray burns had developed on the skin, with spotty epilation of the scalp. By 6 wk, the leukocyte count had dropped to 3,900/mm^3 with depression of both neutrophil and lymphocyte count, and the platelet count had reached a low of 140,000/mm^3 at 30 days. There was a gradual return of these blood elements to near normal levels and a healthy state until 13 yr of age, when benign adenomas of the thyroid gland were detected and removed. At an annual examination at 19 yr of age, the leukocyte count was 2,000/mm^3, but there were no other noteworthy findings. Bone marrow examinations, however, revealed acute myelogenous leukemia. Compatible platelet transfusions were not available to combat severe thrombocytopenia and death from extensive pulmonary bleeding intervened before a remission could be achieved. Comparison of this patient's peripheral blood leukocyte counts with those of eight other boys exposed at less than 5 yr of age and eight unexposed Marshallese boys showed a greater depression of neutrophil count in the leukemia case both during the immediate postexposure period and during subsequent years. None of the individuals in the comparison groups had similarly low levels. Increased chromosome breakage (11% of the cells) that may have been related to radiation exposure or to the disease was noted terminally. Although the occurrence of one case of leukemia in this population is not statistically strong evidence of radiation induction, it is suggested that it must be seriously considered. The ratio of incidence of radiation-induced to otherwise-caused cases indicates that the Marshallese case was about 5-15 x more likely to have been radiation-induced than spontaneous.

3772 ADULT THYROID CANCER AFTER HEAD AND NECK IRRADIATION IN INFANCY AND CHILDHOOD. (Eng.) Becker, F. O. (1753 W. Congress, Chicago, Ill. 60612); Economou, S. G.; Southwick, H. W.; Eisenstein, R. *Ann. Intern. Med.* 83(3):347-351; 1975.

The surgical-pathologic findings in 15 adults who had had a history of irradiation to the head and neck in childhood are reported. These patients were selected for thyroid surgery because of a "cold" area or areas detected on ^{99m}Tc thyroid scan, with or without palpable thyroid abnormalities. Eight of the 15 patients had thyroid cancer, and three had atypical adenomas. Multiple lesions were found in 12 patients. Macroscopic and microscopic malignancy in a location different from the cold area or areas occurred in 5 of the 8 cancer patients. In view of these findings, the authors recommend that adults who received irradiation to the head and neck in childhood and who have been found to have an abnormal thyroid scan or thyroid examination, or both should have a total thyroidectomy.

3773 CANCER MORTALITY FOLLOWING IRRADIATION IN INFANCY FOR HEMANGIOMA. (Eng.) Li, F. P. (Natl. Cancer Inst., Field Station, 35 Binney St., Boston, Mass. 02115); Cassady, J. R.; Barnett, E. *Radiology* 113(1):177-178; 1974.

Three cancer deaths were found (*versus* 2.4 expected) in a record-linkage study of 4,746 patients irradiated in infancy for hemangioma of the skin. The roster came from the Children's Hospital Medical Center, Boston, 1946-1968 and was matched against the names of children who died from cancer, 1960-1968. The total dose in nearly all cases was 300-600 R from a 50 kVp orthovoltage unit. Only one tumor, a testicular teratoma, arose in proximity to the treatment field and may have been induced by radiation. The findings show no significant excess cancer deaths following low-level irradiation, but occurrence of non-lethal cancers of the skin or other organs was not evaluated.

3774 THE SUBCELLULAR DISTRIBUTION OF ^{239}Pu IN RAT LIVER PARENCHYMAL CELLS AFTER EXPOSURE *IN VIVO* AND *IN VITRO*. *(Eng.)* Gurney, J. R. (Inst. Cancer Res., Sutton, Surrey SM2 5PT, England); Taylor, D. M. *Health Phys.* 29(5):655-661; 1975.

The uptake and subcellular distribution of plutonium-239 in L5178Y murine leukemia cells and in suspensions of rat liver parenchymal cells exposed to the nuclide *in vitro* and in similar suspensions prepared from the livers of rats previously injected with plutonium-239 were studied. The stock solution of plutonium-239 had a concentration of 6.5 mg (400 μCi)/ml 3N HNO_3. To 5-μCi aliquots of this solution were added 5 ml of 1.3 mM sodium citrate, and the solution was allowed to stand for 24 hr at 4 C. The solution was either injected iv into rats (4 μCi/animal) four days before sacrifice for the *in vivo* experiments, or added at a concentration of 0.2 μCi/100 ml to the culture medium one hour after the start of incubation. The L5178Y cells were homogenized in 1 mM sodium bicarbonate. The liver cells were suspended in ice-cold 0.25 M sucrose; 0.1 ml of the 105,000 x *g* supernatant from a 20% liver homogenate was added to reduce mitochondrial fragility; and the cells were homogenized in a sonicator at an amplitude of 9 μm for four seconds. The homogenates were subjected to fractionation by differential centrifugation at 2-4 C, and radioactivity was assayed by liquid scintillation counting. The uptake of plutonium-239 by isolated liver cells or by L5178Y cells after being exposed to the nuclide for 24 hr in culture ranged from 0.6-1.5% of the total plutonium-239 added to the medium/10^6 cells. There were considerable differences in the subcellular distribution between liver cells exposed to plutonium-239 *in vitro* and *in vivo*. Following *in vivo* exposure the highest specific activity was found in the lysosomal fraction; after exposure *in vitro*, however, the highest specific activity was found in the nuclear fraction. A similar association of

plutonium-239 with the nuclear and cell debris fractions was observed in the L5178Y cells following exposure to the nuclide *in vitro*. It is concluded that it is not possible to extrapolate from results obtained from studies on the interaction between plutonium and tissues *in vitro* to mechanisms by which cells and tissues handle plutonium *in vivo*.

3775 INDUCTION OF SKIN TUMORS IN HAIRLESS MICE BY A SINGLE EXPOSURE TO UV RADIATION. (Eng.) Hsu, J. (Coll. Phys. Surg., Columbia Univ., New York, N.Y.), Forbes, P. D.; Harber, L. C.; Lakow, E. *Photochem. Photobiol.* 21(3):185-188; 1975.

Circumstances under which UV treatment alone might produce skin tumors in hairless mice were investigated. In total, 127 hairless mutant mice were irradiated and 59 others served as controls. The UV sources were fluorescent sun lamps emitting UV radiation principally in the 280-320 nm range. Single (skin surface) doses of 3×10^4 J/m^2 to 24×10^4 J/m^2 were delivered in three hr or less. Following exposure, mice were examined daily for 14 days, and once wkly thereafter for periods ranging from 70 to 280 days. Mice exposed to low doses of UV radiation developed erythema and edema within 24 hr. Ulcerations were noted after 48 hr on the dorsal surface and head of those mice receiving more than 6×10^4 J/m^2. The higher doses resulted in more severe acute damage as well as in greater tumor yield. Most of the tumors were benign hyperplastic epithelial papillomas; 4/96 tumors examined histologically proved to be squamous cell carcinomas. It is concluded that tumors can be induced by a single dose of UV, but that the dose must be great enough to produce significant tissue damage. Qualitatively, this study indicates that UV can act as a complete carcinogen without an absolute requirement for exogenous promotion; quantitatively, the data show that induction of malignant growths by a single UV exposure is an event of low probability.

3776 THE EFFECT OF A MAMMALIAN REPAIR ENDONUCLEASE ON X-IRRADIATED DNA. (Eng.) Tomura, T. (ULCA Center for Health Sciences, Los Angeles, Calif. 90024); Van Lancker, J. L. *Biochim. Biophys. Acta* 402(3):343-350; 1975.

The effects of mammalian repair endonuclease on DNA extracted from the livers of X-irradiated (1,500 or 3,000 rads total body irradiation) and on purified, X-irradiated (20,000 rads) DNA *in vitro* were studied. The effect of endonuclease on irradiated and nonirradiated DNA was tested by: sedimentation of the DNA in neutral and alkaline sucrose gradients; ^{32}P release after the sequential action of endonuclease and alkaline phosphatase, release of the acid-soluble material after sequential attack of the DNA with endonuclease, alkaline phosphatase, and DNA polymerase in the absence of triphosphates; and incorporation of triphosphates after the sequential treatment of DNA with endonuclease, alkaline phosphatase, and DNA polymerase. Treatment of nonirradiated DNA with endonuclease did not alter the sedimentation pattern on either alkaline or neutral sucrose gradients. The altered patterns seen after endonuclease treatment of irradiated DNA suggested the formation of single strand breaks and an increase in double strand breaks. A dose-dependent release of acid-soluble material was observed following treatment of irradiated DNA with endonuclease, alkaline phosphatase, and DNA polymerase. ^{32}P-labeled DNA irradiated *in vitro* and *in vivo* also acted as a substrate for the repair endonuclease, and the ability of irradiated DNA to serve as a primer for DNA polymerase was increased by repair endonuclease, alkaline phosphatase, and DNA polymerase treatment. The data suggest that in addition to strand breaks, X-irradiation causes base damage, which may be the target of the endonuclease.

3777 COMPARISON OF FREQUENCIES OF RADIATION-INDUCED CHROMOSOME ABERRATIONS IN SOMATIC AND GERM CELLS OF THE RHESUS MONKEY [abstract]. (Eng.) van Buul, P. P. W. (Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, 62 Wassenaarseweg, Leiden, The Netherlands). *Int. J. Radiat. Biol.* 27(6):589-590; 1975.

3778 REPAIR REPLICATION AND ITS DISTRIBUTION IN "NORMAL" AND CANCEROUS HUMAN LYMPHOBLASTOID CELL LINES AFTER PHYSICAL AND CHEMICAL DAMAGE [abstract]. (Eng.) Meltz, M. L. (Southwest Found. Res. Educ., San Antonio, Tex.); Thornburg, W. H. *Radiat. Res.* 62(3):533; 1975.

3779 EFFECT OF INHIBITION OF RNA AND OF PROTEIN SYNTHESIS ON RECOVERY FROM RADIATION-INDUCED DIVISION DELAY [abstract]. (Eng.) Leeper, D. B. (Thomas Jefferson Univ., Philadelphia, Pa.) *Radiat. Res.* 62(3):538; 1975.

3780 AGE-SPECIFIC MORTALITY RATES AND PREVALENCE FREQUENCIES FOR TWO LYMPHOMA TYPES, AND FOR LETHAL AND NONLETHAL PULMONARY TUMORS IN THE BCF_1 MOUSE [abstract]. (Eng.) Sacher, G. A. (Div. Biol. Med. Res., Argonne Natl. Lab., Ill.); Fry, R. J. M.; Tyler, S. A.; Ainsworth, E. J.; Lombard, L.; Staffeldt, E. F.; Allen, K. H. *Radiat. Res.* 62(3):595; 1975.

3781 THE TOXICITY OF INHALED $^{239}PuO_2$ IN IMMATURE, YOUNG ADULT, AND AGED SYRIAN HAMSTERS [abstract]. (Eng.) Hobbs, C. H. (Inhalation Toxicology Res. Inst., Lovelace Foundation, Albuquerque, N.M.); Mewhinney, J. A.; Slauson, D. O.; McClellan, R. O.; Miglio, J. J. *Toxicol. Appl. Pharmacol.* 33(1):194-195; 1975.

3782 LEUKEMOGENIC EFFECT OF HEAVY IONS IN RF MICE (CARBON-ION BEAM 250 MeV/amu) [abstract). (Eng.) Kelly, L. S. (Lawrence Berkeley Lab., Univ. Calif.); Daniels, S. J.; LaPlant, P. R.; Thomas, R. H. *Radiat. Res.* 62(3):595; 1975.

3783 SCANNING ELECTRON MICROSCOPY OF MAMMALIAN CELLS TRANSFORMED *IN VITRO* BY X-RAYS [abstract]. (Eng.) Borek, C. (Coll. Physicians Surg., Columbia Univ., New York, N.Y.); Fenoglio, C. *Radiat. Res.* 62(3):596; 1975.

3784 CHARACTERIZATION OF THE ONCO-FETAL PROTEIN ISOLATED FROM RADIATION-INDUCED RAT SMALL BOWEL ADENOCARCINOMAS [abstract]. (Eng.) Stevens, R. H. (Radiat. Res. Lab., Univ. Iowa, Iowa City); Englund, C. W.; Cheng, H. F.; Osborne, J. W. *Radiat. Res.* 62(3):603-604; 1975.

3785 DISTRIBUTION STUDIES OF ANTIMONY RADIONUCLIDES [abstract]. (Eng.) Spencer, R. P. (Univ. Connecticut Health Cent., Farmington); Miller, R. E.; Lange, R. C.; Ayoub, T. *Fed. Proc.* 34(3):266; 1975.

3786 IRRADIATION OF THE NECK DURING CHILDHOOD: AN ASSESSMENT OF FACTORS WHICH INFLUENCE THE DEVELOPMENT OF THYROID TUMORS IN PERSONS AT RISK [abstract]. (Eng.) Colman, M. (Michael Reese Med. Cent., Chicago, Ill.); Simpson, L. R.; Patterson, L. K.; Ovadia, J. *Radiat. Res.* 62(3):599; 1975.

3787 HEPATIC RADIATION INJURY: EARLY AND LATE [abstract]. (Eng.) Kinzie, J. J. (Dept. Radiol., Univ. Chicago, Ill.); Swartz, H.; Hensley, G.; Griem, M. L. *Radiat. Res.* 62(3):543; 1975.

See also:

* (Rev): 3611, 3612, 3613, 3628, 3643, 3644, 3645, 3650, 3653
* (Immun): 3911, 3935, 3947, 3982
* (Path): 3991, 4003, 4026, 4037
* (Epid-Biom): 4113

3788 STRUCTURAL PROTEINS OF ADENOVIRUSES: XII. LOCATION AND NEIGHBOR RELATIONSHIP AMONG PROTEINS OF ADENOVIRION TYPE 2 AS REVEALED BY ENZYMATIC IODINATION, IMMUNOPRECIPITATION AND CHEMICAL CROSS-LINKING. (Eng.) Everitt, E. (Wallenberg Lab., Univ. Uppsala, Uppsala, Sweden); Lutter, L.; Philipson, L. *Virology* 67(1):197-208; 1975.

A typographical model of adenovirus type 2 was constructed based on results with enzymatic iodination of intact and disrupted virions, immunoprecipitation of intact virions with specific antisera, and crosslinking with reversible chemical crosslinkers to reveal adjacent proteins. Material from sonically treated isolated nuclei of productively infected HeLa cells was iodinated and the labeled virus purified by a procedure causing a minimum of damage to the virions. The sodium dodecyl sulfate-polyacrylamide-gel electrophoresis pattern of labeled polypeptides of intact virions was compared to the pattern obtained after labeling pyridine-disrupted virions. In the immunoprecipitation experiments, the virus material was labeled with [^{3}H]thymidine and immunoprecipitation was carried out with a direct and a double antibody technique. Crosslinking experiments were performed using the cleavable protein crosslinker, tartaryl diazide, which is capable of crosslinking protein amino groups which are at most 0.6 nm from each other. In iodinated intact virions most of the label was confined to hexons, fibers and to some extent to penton bases. After the virions had been frozen and thawed once, the iodine label was also present in polypeptides V and VII and to a lesser extent in polypeptide VI, suggesting that adenovirions are not rigid entities. Virions disrupted with pyridine were labeled in all polypeptides except in polypeptide IX. Antisera against proteins IIIa and IX precipitated virions with the double antibody technique but these proteins failed to become labeled in intact virions. The efficient precipitation of virions with anti-IIIa suggests an external location. Antisera against proteins VI-VIII did not precipitate virions and the corresponding polypeptides were not iodinated in intact virions. Two new electrophoretic components appeared following crosslinking: one composed of polypeptides V and VII and the other a dimer of polypeptide VII. A complex of IIIa and VII, a dimer of polypeptide VI, and a complex consisting of polypeptides V and VI were also detected. These results suggest that proteins VI, VII, and VIII are located within the virion, that the core protein V is also an internal protein probably located at the vertices in close connection with the penton bases, hexons, and protein IIIa molecules, and that proteins IIIa and IX lack tyrosine residues exposed on the outside of the virion but have external antigenic determinants.

3789 HUMAN CELLS REPAIR DNA DAMAGED BY NITROUS ACID. (Eng.) Day, R. S., III, (Natl. Cancer Inst., Bethesda, Md.). *Mutat. Res.* 27(3):407-409; 1975.

The ability of human cells to repair DNA damaged by nitrous acid was tested. Adenovirus 2 stock (0.1 ml) containing 3 x 10^7 plaque-forming U/ml was treated at 37 C for periods up to 16-20 min with 1M $NaNO_2$ (0.6 ml) at pH 5.0, in 0.25 M $NaC_2H_3O_2$. Samples were titered on cultured fibroblasts obtained from normal subjects (strains KD, ND, and HG800) and from subjects with xeroderma pigmentosum (strains XP, LO, $XP_{12}BE$, and XP_4BE). With three of the four xeroderma pigmentosum strains at hosts, $NaNO_2$-damaged virus showed only half the plaque-forming ability of the normal strains. This indicates that DNA damaged by nitrous acid is at least partly repaired by normal human cells.

3790 STRUCTURE AND COMPOSITION OF THE ADENOVIRUS TYPE 2 CORE. (Eng.) Brown, D. T. (Inst. Genetics, Univ. Cologne, Cologne, Germany); Westphal, M.; Burlingham, B. T.; Winterhoff, U.; Doerfler, W. *J. Virol.* 16(2):366-387; 1975.

The structure and composition of the core of adenovirus type 2 were analyzed by electron microscopy and biochemical techniques after differential degradation of the virion by heat, by pyridine, or by sarcosyl treatment. In negatively stained preparations purified sarcosyl cores revealed spherical subunits 21.6 nm in diameter in the electron microscope. It is suggested that these subunits are organized as an icosahedron that has its axes of symmetry coincident with those of the viral capsid. The subunits were connected by the viral DNA molecule. The sarcosyl cores contained the viral DNA and predominantly the arginine/alanine-rich core polypeptide VII. When sarcosyl cores were spread on a protein film, tightly coiled particles were observed; these gradually unfolded giving rise to a rosette-like pattern due to the uncoiling DNA molecule. Completely unfolded DNA molecules were circular. Pyridine cores consisted of the viral DNA and polypeptides V and VII. In negatively stained preparations of pyridine cores, the subunit arrangement apparent in the sarcosyl cores was masked by an additional shell which was probably formed by polypeptide V. In freeze-cleaved preparations of the adenovirion, two fracture planes were recognized. One fracture plane probably passed between the outer capsid of the virion and polypeptide V exposing a subviral particle that corresponded to the pyridine core. The second fracture plan observed could be located between polypeptide V and the polypeptide VII-DNA complex, thus uncovering a subviral structure that corresponded to the sarcosyl core. In the sarcosyl core, polypeptide VII was tightly bound to the viral DNA, which was susceptible to digestion with DNase (1 μg/ml). The restriction endonuclease EcoRI cleaved the viral DNA in the sarcosyl cores into the six specific fragments. These fragments could be resolved on polyacrylamide-agarose gels provided the sarcosyl cores were treated with pronase (5 mg/ml) after incubation with the restriction endonuclease. When pronase digestion was omitted, a complex of the terminal EcoRI fragments of adenovirus DNA and protein could be isolated. From this complex, the terminal DNA fragments could be liberated after pronase treatment. The complex described is presumably responsible for the circularization of the viral DNA inside the virion. The nature of the

protein(s) involved in circle formation has not yet been elucidated.

3791 BIOCHEMICAL STUDIES ON BOVINE ADENOVIRUS TYPE 3: I. PURIFICATION AND PROPERTIES. (Eng.) Niiyama, Y. (Biological Res. Lab., Central Res. Div., Takeda Chemical Industries, Ltd., Osaka, Japan); Igarashi, K.; Tsukamoto, K.; Kurokawa, T.; Sugino*, Y. *J. Virol.* 16(3):621-633; 1975.

Bovine adenovirus type 3 (BAV3) was purified, and its properties were studied. On productive infection of CKTl cells (a cell line derived from calf kidney) with BAV3, viral DNA synthesis was initiated after about 24 hr, and its rate was maximal after about 40 hr. Maturation of the virus occurred several hours after this. Purified BAV3 was separated into four discrete bands by CsCl density gradient centrifugation (complete, incomplete, empty, and degraded viruses). The complete BAV3 was similar in size and structure to human and avian adenoviruses. Polyacrylamide gel electrophoresis showed that the complete BAV3 virion contained at least ten polypeptides. The total structural proteins of the virion had a similar amino acid composition to those of human adenoviruses. DNA of the complete virus was a linear duplex and its contour length was 12.3 ± 0.9 μm. The sedimentation coefficient of the DNA was 32.9S, and its buoyant density in CsCl was 1.717 g/ml. There was about 25% homology between the DNAs of BAV3 and human adenovirus type 5 by filter hybridization. It was also noted that BAV3 produced incomplete virus. The incomplete virus was similar in morphology to the complete virus and contained almost all the structural polypeptides of the latter, but lacked infectivity. However, its DNA had about 3% deletion(s), which seemed to locate near a terminal.

3792 GROWTH OF ADENO-ASSOCIATED SATELLITE VIRUS UNDER CONDITIONS OF ARGININE DEPRIVATION. (Eng.) Mayor, H. D. (Baylor Coll. Medicine, Houston, Tex. 77025); Gorman, C. *Virology* 66(1):25-35; 1975.

African green monkey kidney cells were infected with adeno-associated satellite viruses type 4 and type 1 and simian adenovirus SV15 during arginine deprivation and under normal conditions and density gradient profiles of radioactively labeled satellite particles were correlated with hemagglutination, biological activity and physical conformation of satellite virus particles. Simian adenovirus SV15 helper adenovirus was used at 10 PFU/cell and adeno-associated satellite virus type 4 at 10 hemagglutinin-producing U/cell. Six hours after inoculation, [^{3}H]thymidine (50 μCi/culture) was added. Viruses were harvested after three cycles of freezing and thawing. Identical experiments were carried out using adeno-associated satellite virus type 1 at 10 complement fixing U/cell. Satellite virus infectivity was assayed by the ability to produce heat-stable hemagglutinin in the presence of satellite-free helper simian adenovirus SV15 in the kidney cells. Virus harvests were subjected to density gradient analysis in 5-ml gradients of CsCl and the fractions assayed for [^{3}H] radioactivity by liquid scintillation counting. Virus particles were identified and categorized by electron microscopy. No complete adenoviruses were seen in the electron microscope in harvests prepared under arginine-free conditions. Although fewer physical satellite particles (5×10^{10} satellite virus particles/ml compared to 1.3×10^{12} in arginine-rich medium) were produced under arginine-free conditions and their morphology was less regular, their particle/-infectivity ratio ($10^{6.8}$ hemagglutinin-producing U/ml) was not significantly different from that of satellite progeny ($10^{8.8}$ hemagglutinin-producing U/ml) isolated from arginine-rich conditions in which adenoviruses were also demonstrated. The satellite particles isolated from arginine-free medium, although originally infectious, lost infectivity rapidly and were less stable morphologically than satellite viruses produced under standard nutritional conditions. Satellite particles were visualized in both the nucleus and cytoplasm indicating that transport of viral components is not inhibited. Type 4 satellite virus particles harvested from arginine-free growth conditions lacked the hemagglutinin normally associated with the mature type 4 virion, which may indicate that certain structural proteins are missing.

3793 REGIONAL LOCALIZATION OF HUMAN GENES IN VIRUS-INDUCED UNCOILER REGIONS. (Eng.) McDougall, J. K. (Dept. Cancer Studies, Univ. Birmingham, Birmingham, Conn.); Elsevier, S. M.; Kucherlapati, R. S.; Ruddle, F. H. *Cytogenet. Cell Genet.* 14(3-6):202-204; 1975.

Previous studies on adenovirus 12-infected mouse-man hybrid cells containing only the long arm and the centromere region of human chromosome 17 enabled localization of the thymidine kinase (TK) gene to the virus-induced uncoiler region. In the present study, the localization of galactokinase (GaK) of an adenovirus 12-infected hybrid cell line derived by Sendai virus-mediated fusion of normal human fibroblasts and mouse L cells deficient in TK was investigated. Subclones previously shown to have lost TK activity and the portion of the chromosome 17 distal to 17q21 were negative for human GaK. Those subclones retaining a larger portion of the long arms, but which are deleted distal to the break in 17q22, retained both human TK and GaK activity. Thus, the genes for both these enzymes must be located in the uncoiler regions between the two break points and are therefore assigned to human chromosome 17, band q21-22. Studies are in progress to determine whether a virus-coded DNA-binding protein may be the mediator of the uncoiling effect.

3794 CELL-TO-CELL ATTACHMENTS AND ASSOCIATIONS IN TUMORS INDUCED BY CELO VIRUS OR VIRUS-TRANSFORMED CELLS IN HAMSTERS. (Eng.) Jasty, V. (Dept. Toxicology, Sterling-Winthrop Res. Inst., Rensselaer, N.Y. 12144); Pendola, R.; Yates, V. J. *Am. J. Vet. Res.* 36(11):1643-1648; 1975.

Cell-to-cell attachments or associations in experi-

mentally induced sarcomas of chicken embryo lethal orphan virus (avian adenovirus) origin were studied in hamsters by electron microscopy. The tumors were induced by sc inoculation of the small-plaque variant of the virus into newborn hamsters or by sc inoculation of hamster embryo cells transformed *in vitro* by palque variants of the virus into weanling hamsters. In virus-induced tumors, the cell-to-cell attachments and associations depended mainly on the cell density present in a given area of the tumor. Where tumor cells were closely packed, the adjacent cells were related to each other by noninterdigitating plasma membranes of uniform thickness, closely apposed to each other but separated by a distance of 20-25 nm. Specialized focal cell-to-cell attachments were frequently observed along the parallel-running plasma membranes; in many instances, the attachment sites resembled desmosome-like structures. Less frequently, the cells were attached by button-like projections between the cell surface. In transformed cell-induced tumors, the most common intercellular relationship was the interlocking of the apposing plasma membranes. Cell-to-cell attachments resembling desmosome-like structures and button-like projections were also observed in these tumors. In rare instances, adjacent cells were held together by interdigitating filopodia present on their free surfaces. The wide spectrum of cell-to-cell associations observed in this study is indicative of a poor cell-to-cell communication system that distinguishes transformed cells from their normal counterparts.

3795 PRODUCTION BY EBV INFECTION OF AN EBNA-POSITIVE SUBLINE FROM AN EBNA-NEGATIVE HUMAN LYMPHOMA CELL LINE WITHOUT DETECTABLE EBV DNA. (Eng.) Clements, G. B. (Karolinska Inst., S-104 01 Stockholm 60, Sweden); Klein, G.; Povey, S. *Int. J. Cancer* 16(1):125-133; 1975.

The establishment and characteristics of a continuous lymphoma cell line, BJAB, derived from the tumor of an exceptional African case of Burkitt's lymphoma (BL), are described. Unlike 97% of African BL cases previously studied, neither the original tumor cells nor the cell line contained detectable amounts of Epstein-Barr virus (EBV) DNA, nor did they express the EBV-determined nuclear antigen (EBNA). The cells of the established line had the characteristics of B-type lymphocytes and they carried receptors for EBV. EBNA was induced in the majority of BJAB cells after EBV infection. Usually the cells died within ten days of infection, but it was possible to establish a permanent EBNA-positive variant (GC-BJAB) of BJAB. The patient from whose tumor the original BJAB line was established was seropositive for EBV antigens, indicating previous exposure to and continuing presence of the virus; yet the tumor had not become infected by EBV. This evidence shows that EBV is not readily "picked up" by the lymphoma.

3796 TARGET CELL FOR ONCOGENIC ACTION OF POLYCYTHAEMIA-INDUCING FRIEND VIRUS. (Eng.) Tambourin, P. E. (Unite de Physiologie Cellulaire de l'INSERM, (Institut du Radui) Vatiment 110, 91405 Orsay, France); Wendling, F. *Nature* 256(5515):320-322; 1975.

The ability of hematopoietic stem cells to give rise to differentiated colonies in the spleen of irradiated syngenic recipients was used to determine whether the multipotent stem cell of the hematopoietic system is the target cell for polycythemia-inducing Friend virus (FVP). Hypertransfused, irradiated C3H/Hemg mice were grafted with 3 x 10^5 syngenic normal spleen cells; on days 2, 4, or 6 after the graft they were inoculated iv with 0.2 ml of highly infectious plasma (10^5 focus-forming U) from polycythemic mice infected with FVP. Spleen sections from the inoculated mice were stained with diorthanisidine, an indicator of Hb peroxidase activity, and with azur B and fuschin for detecting basophilic and acidophilic cells. Hb synthesis was also investigated by autoradiographic determination of ^{55}Fe (45 μCi/mouse, iv) incorporation. Spleens of mice injected with FVP on day 4 after grafting and harvested on day 7 contained differentiated neutrophilic, megakaryocytic, and eosinophilic colonies. There were also small colonies of hyperbasophilic Friend cells containing basophilic and some polychromatophilic erythroblasts. The labeling of both hyperbasophilic Friend cells and erythroblasts. The labeling of both hyperbasophilic Friend cells and erythroblasts in autoradiograms confirmed the initiation of Hb synthesis. Spleens of mice killed on day 9 after grafting (on day 3 after virus infection) contained similar but larger colonies. In both groups of mice, the distribution of the various histologic types of colonies was not significantly different from the distribution in spleens of nonplethoric mice receiving the same spleen cell suspension. Spleens of mice inoculated with virus on day 2 and killed on day 5 after the graft contained small clusters of hyperbasophilic Friend cells in association with young basophilic erythroblasts only. Twenty-four hours earlier, no hyperbasophilic Friend cells could be observed. These results indicate that (a) the multipotent hematopoietic stem cell is not the target cell for FVP, (b) the viral gene that induces transformation can be expressed only in an erythroid committed cell (the erythropoietin-response cell or a closely related precursor, and (c) only the erythroid pathway of differentiation is open to hyperbasophilic Friend cells.

3797 EFFECT OF RIFAMYCIN AND TILORONE DERIVATIVES ON FRIEND VIRUS LEUKEMIA IN MICE. (Eng.) Rana, M. W. (Saint Louis Univ. Sch. Medicine, St. Louis, Mo. 63104); Pinkerton, H.; Rankin, A. *Proc. Soc. Exp. Biol. Med.* 150(1):32-35; 1975.

The ability of rifamycin derivatives and tilorone-fluoranthene analogs to inhibit splenomegaly in Friend virus leukemia was examined in 542 BALB/c mice injected in the retroorbital plexus with 0.05 ml of mouse serum containing Friend leukemia virus (3.71 spleen-enlarging U/ml). Rifamycin derivatives were dissolved in dimethylsulfoxide and injected into groups of 10 mice sc at 13.5 mg/kg (i.e., 20 ng/ml mouse fluid). Tilorone-fluoranthene agents were given sc in aqueous solution at 50 mg/kg. The injections, usually 30 min before or 30 min after the

virus, were given on days 0, 1, 2, and 14, 15, 16. Controls received virus alone or (positive controls) methotrexate (1.4 mg/kg). Mice given virus alone had average spleen weights of 520-110 mg, depending largely on the time each experiment was terminated. Methotrexate-treated mice uniformly showed 90-92% inhibition of splenomegaly. Results were variable with the rifamycin derivatives and the tilorone-fluoranthene analogs, but three members of the rafamycin group (C20, C23, and C11) significantly inhibited splenic enlargement (31-49%) as did three members of the tilorone group (tilorone HCL, M5, and MT; 32-48% inhibition). The six inhibitory compounds are among those previously found to be most inhibitory *in vitro* to the RNA-directed DNA polymerase of oncornaviruses. However, no direct evidence was obtained for or against a role of inhibition of the viral enzyme in the suppression of splenomegaly. Spleen weight inhibition was 40% when C23 was given three hours before virus, and 38% when it was given three hours after virus (i.e., after transformation of spleen hemopoietic cells). Thus, viral enzyme inhibition was apparently not the major mechanism by which this agent inhibited splenomegaly. C23, C20, and M5 had a subtractive effect on the inhibition caused by methotrexate alone. *Mycobacterium butyricum* (0.2 ml/mouse, sc) and pertussis vaccine (0.15 ml/mouse, sc.) reduced, rather than enhanced, the activity of C23, C31, M7, and methotrexate.

3798 PROPERTIES OF CELL LINES DERIVED FROM TUMORS INDUCED BY FRIEND VIRUS IN BALB/c AND BALB/c-*H*-2^b MICE. (Eng.) Freedman, H. A. (Albert Einstein Coll. Medicine, Bronx, N. Y. 10461); Lilly, F. *J. Exp. Med.* 142(1):212-223; 1975.

The effect of the *H*-2 locus on the Friend virus (FV) disease was studied in a series of experiments with tumor cells induced with FV in BALB/c (*H*-2^d) and congenic BALB/c-*H*-2^b (BALB.B) mice. Spleens from virus-infected hosts in the terminal stages of erythroleukemic disease provided tissues for the establishment of sc-transplantable tumors of both strains. Subsequently, cells of these tumors were introduced into culture and passed serially. Complete, infectious Friend virus (FV) was routinely recovered from culture supernates of BALB.B tumor cells (HFL/b) throughout its 2-yr passage history. However, after only a few transfer generations in culture, BALB/c tumor cells (HFL/d) became nonproducers of virus detectable in either the spleen focus assay *in vivo* or the XC assay *in vitro*. Nonproducer HFL/d cells possessed the complete genomes of the components of the FV complex, since FV could be recovered from them either by cocultivation with helper virus-infected syngeneic embryo fibroblasts or by serial passage in the ascitic form in normal, syngeneic adult hosts.

3799 POLY(A) POLYMERASES IN NORMAL AND VIRUS-TRANSFORMED CELLS. (Eng.) Pellicer, A. (Departmento de Biologia Molecular, Instituto G. Marañon, Centro de Investigaciones Biolgicas, C.S.I.C. Velazquez, 144, Madrid-6, Spain); Salas, J.; Salas, M. L. *Biochim. Biophys. Acta* 378(1):107-118; 1975.

The presence of poly(A) polymerases was studied in a clone of the established hamster embryo fibroblast line NIL, and in a subclone of the line transformed by virus hamster sarcoma (HS) virus. DEAE-cellulose chromatography revealed three peaks of activity of the DNA-cellular wash fractions from stationary NIL and NIL-HS virus cell; differences in their catalytic activities suggested the existence of three distinct poly(A) polymerases, designated I, IIA, and IIB. Phosphocellulose chromatography of polymerases I and II from growing NIL-HS virus cells revealed polymerase I binding to the column; polymerase IIA did not bind, while polymerase IIB was bound to the phosphocellulose and was eluted. Experiments performed with the enzyme from growing NIL-HS virus illustrated the 6-fold higher incorporation of [^{3}H]ATP by nucleotidyltransferase with MN^{2+} than with Mg^{2+}. In contrast, the incorporation of [^{3}H] cytosine triphosphate (CTP) in the presence of Mn^{2+} was only 80% of that with Mg^{2+}. The average chain length of the products of the various poly(a) polymerases was calculated as 4, 50, and 20 nucleotide residues for polymerase I, IIA, and IIB, respectively. The product synthesized by nucleotidyltransferase, in the presence of Mg^{2+} or Mn^{2+}, was almost completely degraded by RNase. The products of polymerase I, IIA, and IIB were highly RNase-resistant. The three polymerases illustrated different requirements for divalent cations; all of the poly(A) polymerases were highly specific for ATP. The finding that poly(A) was an effective primer for the three polymerases indicate the importance of the length of the poly(A) sequence for printing activity. It is suggested that poly(A) polymerases may play a role in the post-transcriptional addition of poly(A) sequences to the 3' terminus of messenger RNAs.

3800 BASE SEQUENCE DIFFERENCES BETWEEN THE RNA COMPONENTS OF HARVEY SARCOMA VIRUS. (Eng.) Maisel, J. (Dept. Molecular Biology and Virus Lab., Univ. California, Berkeley, Calif. 94720); Scolnick, E. M.; Duesberg*, P. *J. Virol.* 16(3):749-753; 1975.

The large (component 1) and the small (component 2) 30-40S RNA species were isolated from the Harvey sarcoma-Moloney leukemia virus complex by preparative gel electrophoresis. Harvey RNA component 1 was completely complementary to DNA transcribed from Moloney leukemia virus (MLV) RNA and showed no homology to DNA transcribed from a C-type rat virus (NRK) when annealed under conditions of DNA excess. Harvey RNA component 2 was about 65% complementary to MLV DNA and about 33% complementary to NRK virus DNA. Approximately 60-80% of the MLV-specific sequences in RNA component 2 was either a distinct molecular species or was part of a hybrid molecule including NRK virus- and MLV-specific sequences. The rest of the MLV sequences in component 2 could be accounted for by degraded component 1 copurifying with component 2. The possible role of these sequences in the ability of the virus to transform cells is discussed.

3801 POLYPEPTIDES SYNTHESIZED IN HERPES SIMPLEX VIRUS TYPE 2-INFECTED HEp-2 CELLS. (Eng.) Powell, K. L. (Baylor Coll. Medicine, Houston, Tex.

77025); Courtney, R. J. *Virology* 66(1):217-228; 1975.

The proteins induced by herpes simplex virus type 2 in infected HEp-2 cells were studied by high-resolution polyacrylamide slab-gel electrophoresis. A total of 51 infected cell-specific polypeptides (ICSP) were detected, accounting for three-fourths of the coding capacity of the virus. The induced polypeptides were allocated to three groups based on their time of synthesis in the virus growth cycle. Cycloheximide treatment (50 μg/ml) of infected cells during the early stage of virus growth was found to cause irreversible inhibition of protein synthesis. Herpes simplex virus 2 polypeptides that underwent considerable posttranslational modification were detected.

3802 *IN VITRO* SYNTHESIS OF DNA IN NUCLEI ISOLATED FROM HUMAN LUNG CELLS INFECTED WITH HERPES SIMPLEX TYPE II VIRUS. (Eng.) Kolber, A. R. (German Cancer Res. Cent., Heidelberg, West Germany). *J Virol.* 15(2):322-331; 1975.

The characteristics of an isolated nuclear system prepared from herpes type II-and mock-infected human embryonic lung cells is described. Human embryonic lung cells were infected with plaque forming unit (PFU) of herpes Type II virus/cell. The cells were incubated and nuclei were prepared and suspended in isoionic HEPES buffer. The *in vitro* reaction mixture consisted of 7 μCi of [^{3}H]dTTP. Incorporation of [^{3}H]TTP in the *in vitro* reaction mixture required Mg^{2+} and ATP. Overall *in vitro* DNA synthesis in nuclei isolated from herpes-infected cells was semiconservative, as demonstrated by bromodeoxyuridine-substituted DNA density transfer experiments, but exhibited a significant fraction of repair type replication. Relative rates of total DNA synthesis *in vitro* and *in vivo* were the same any time after infection with 2 PFU herpes simplex type II virus/cell. Isolated nuclei synthesized cell and viral DNA for a length of time and rate dependent upon the incubation temperature, but there were differences in the length of time of linear *in vitro* DNA synthesis between herpes and mock-infected cells. The temperature optima for *in vitro* DNA synthesis differed significantly for herpes-and mock-infected cells, and were the same for cells abortively infected with herpes type II as for mock-infected cells. An explanation for the stimulation of overall synthesis observed in the herpes isolated nuclei system and *in vivo* may be the induction of a new DNA polymerase coded for by the herpes genome and localized in the nucleus.

3803 FAILURE OF NEUTRAL-RED PHOTODYNAMIC INACTIVATION IN RECURRENT HERPES SIMPLEX VIRUS INFECTIONS. (Eng.) Myers, M. G. (Univ. Iowa Hosp., Iowa City, Iowa 52242); Oxman, M. N.; Clark, J. E.; Arndt, K. A. *N. Engl. J. Med.* 293(19):945-949; 1975.

Because photodynamic inactivation of herpes simplex virus infections may not be free of hazard, the efficacy of photodynamic inactivation with neutral red and light was evaluated in a placebo (phenolsulfonphthalein)-controlled study of 170 episodes of recurrent herpes simplex virus infection in 96 patients. Herpes simplex vesicles were painted with aqueous 0.1% solutions of neutral red or phenolsulfonphthalein and exposed to a 100-watt white incandescent lamp for 15 min at a distance of 26.5 cm. The patients were instructed to repeat the light exposure after 4-6 hr and then again 24 hr later. If new vesicles appeared within 48 hr, they were similarly treated. The neutral red was shown to photoinactivate herpes simplex virus *in vitro*, but had no significant effect on the rate of resolution of herpetic lesions ($P > 0.10$) or on the frequency of subsequent recurrences ($P > 0.10$), except for orolabial lesions, in which an adverse effect on the rate of subsequent recurrences was observed ($P < 0.05$). In the absence of demonstrated efficacy, the routine use of neutral red and light in patients with recurrent herpes simplex virus infections should be discontinued. Furthermore, other photoactive dyes should not be used until their efficacy has been demonstrated by suitably controlled clinical trials.

3804 EFFECTS OF DISCRETE NUCLEAR U.V.-MICROBEAM IRRADIATION ON HERPES VIRUS AND SV40 INFECTION. (Eng.) Deak, I. I. (Sir William Dunn Sch. Pathol., Univ. Oxford, England); Defendi, V. *J. Cell Sci.* 17(3):531-538; 1975.

The requirement for a nucleolus in the expression of structural genes of nuclear viruses was examined in BSC-I cells. The nucleoli and other nuclear components were irradiated by a 4 μm UV beam for seven seconds; whole nuclei were irradiated by a 25 μm beam for the same time. The cells were then exposed to herpes virus type I (20 plaque-forming U/cell) or to 10 plaque-forming U/cell of simian virus 40 (SV40) for one hour at 37 C. Embryonic chick RBC nuclei were fused to BSC-I cells; SV40 viral markers were studied after various nuclear components of the heterokaryons were irradiated. Indirect immunofluorescence measurement of T and V antigens, as well as the measurement of tritiated thymidine uptake in the SV40-infected cells, revealed complete viral-marker inhibition of cells in which the whole nucleus was irradiated. Irradiation of limited regions of the nucleus, including irradiation of a solitary nucleolus within a nucleus, had no effect on the expression of SV40 viral markers. Similarly, whole nucleus irradiation of herpes virus-infected cells prevented the appearance of viral antigens and also of cell surface changes demonstrated by concanavalin A-mediated hemadsorption. Irradiation of any site within the nucleus caused some reduction in the proportion of cells containing viral antigens, but not in the proportion of those expressing other viral antigen markers. There was no significant difference between cells in which a single nucleous was irradiated, and those in which one nucleolus of two within the same nucleus was irradiated or those in which a nucleoplasmic area was irradiated. The proportion of cells synthesizing V antigen did not fall markedly in the irradiated nuclei of heterokaryons, and V antigen appeared in both the BSC-I cells and the RBC nuclei. This suggests that infecting SV40 DNA can enter the RBC nuclei and direct V antigen synthesis in the

cytoplasm of the heterokaryons. The results show that nuclear virus gene expression, unlike cellular gene expression, is not dependent on the nucleolus. SV40 DNA may also enter reactivated chick RBC nuclei in heterokaryons and direct the synthesis of both viral antigen and DNA; these nuclei may thus be rendered permissive to SV40 infection by the BSC-I cytoplasm.

3805 ANATOMY OF HERPES SIMPLEX VIRUS DNA: STRAIN DIFFERENCES AND HETEROGENEITY IN THE LOCATIONS OF RESTRICTION ENDONUCLEASE CLEAVAGE SITES. (Eng.) Hayward, G. S. (Dep. Microbiol., Univ. Chicago, Ill.); Frenkel, N.; Roizman, B. *Proc. Natl. Acad. Sci. USA* 72(5):1768-1772; 1975.

Herpes simplex virus (HSV) was digested by the restriction endonucleases from *Hemophilus influenzae* strain RY13 (*Eco*RI). Electrophoretic study showed that the digests contained fragments with molecular weights from 1 x 10^6 to 28 x 10^6. The electrophoretic profiles obtained in 0.3% agarose gels with DNA fragments from nine different strains of HSV-1 could be readily differentiated from the patterns exhibited by the corresponding fragments from four separate strains of type 2 virus; however, within each serotype, the laboratory strains differed significantly among themselves and also from isolates passaged a minimum number of times outside the human host. Digestion of all DNAs of HSV with either enzyme reproducibly generated two classes of fragments (major and minor) which differed in M concentration. Although the molecular wt of an intact HSV-1(F1) DNA molecule is approximately 98 x 10^6, the summed molecular weights of all major and minor *Hin*III fragments totalled 160 x 10^6, and the seven major fragments alone accounted for only 50 x 10^6. These unusual features indicate the existence of limited heterogeneity in the positions of cleavage sites along individual molecules. Minor fragment patterns were reproducible and remained after plaque purification, whereas defective DNA molecules of high buoyant density appeared only after serial undiluted passaging and were easily eliminated. Thus the minor fragments cannot be attributed to the presence of these defective DNA molecules. This type of DNA was resistant to cleavage by *Hin*III and gave large amounts of only two species of *Eco*RI fragments, suggesting that the defective molecules consist of many tandem repeats of a small segment of viral DNA. The heterogeneity in the viral DNA of normal density appears to be related to the structural organization of the molecules and does not necessarily imply differences in genetic content.

3806 UPTAKE OF [^{3}H] THYMIDINE AND CELL DNA SYNTHESIS DURING THE EARLY MULTIPLICATION PHASE OF HERPESVIRUS HOMINIS IN BHK CELLS. (Eng.) Sittlingmaier, K. (Inst. Medical Microbiology, Univ. Mainz, Mainz, West Germany); Schneider, D.; Falke, D. *Biochim. Biophys. Acta* 407(4):384-391; 1975.

The uptake of ^{3}H-thymidine and its incorporation in cellular DNA of BHK cells during the first six hours after infection with herpesvirus hominis was studied in an attempt to determine if changes in the uptake of percursors might indicate a functional alteration of the cell membrane and consequently might influence cellular metabolism. For most experiments, cells were used 32 hr after seeding in Eagle's medium containing 5% calf serum, 0.5% tryptose phosphate, and buffers. The cells were infected with herpesvirus strains Lennette and IES for 30 min or one hour. The multiplicity of infection was 5-10/cell. After varying periods of time, cells were labeled for 30 or 60 min with ^{3}H-thymidine. The supernatant was discarded, and the cell pellet was resuspended in 0.5 ml 5% trichloracetic acid solution. After ultrasonication for ten seconds, the material was centrifuged for 20 min at 4,000 revolutions/min. Radioactivity was determined in a liquid scintillation spectrometer. During the absorption and penetration period, the inhibition of uptake and of incorporation of ^{3}H-thymidine was sensitive to heat, but not to UV irradiation or cycloheximide treatment. The viral eclipse period was characterized by a strongly increased uptake (8-fold) of ^{3}H-thymidine and by inhibition of cellular DNA synthesis. Both were sensitive to UV irradiation of the particles and cycloheximide treatment of the cells. It is concluded that events during adsorption and penetration are dependent on the particles themselves; events during the eclipse phase, however, depend on the activity of the viral genome. Increased uptake of ^{3}H-thymidine during the eclipse could be the consequence of a general change in pyrimidine metabolism, or could be caused by some virus genome-induced alterations of the cellular membrane.

3807 CHRONIC ANTIGENIC STIMULATION, HERPESVIRUS INFECTION, AND CANCER IN TRANSPLANT RECIPIENTS. (Eng.) Matas, A. J. (Univ. Minnesota Hosp., Minneapolis, Minn. 55455); Simmons*, R. L.; Najarian, J. S. *Lancet* 1(7919):1277-1279; 1975.

The possible relationships of immunosuppression, chronic antigenic stimulation, herpesvirus infection, and increased incidences of lymphoproliferative disorders and carcinomas in transplant recipients are discussed. Unlike cancers in the general population, 75% of the tumors reported in transplant recipients are lymphoproliferative tumors or skin, lip, or cervical carcinomas. The preponderance of the tumors, and the unusual location, behavior, and histology of the lymphoproliferative disorders, suggest that the pathogenesis is not simply due to drug-induced loss of systemic immunosurveillance nor to the immunological privilege of a special site. After noting the experimental demonstration of latent oncogenic RNA viruses, clinical reactivation of latent DNA viruses, especially the herpesvirus, is reported in 70-90% of renal transplant patients. Evidence linking the Epstein Barr virus with Burkitt's lymphoma is cited, and the association of Epstein Barr virus with 85% of the squamous cell nasopharyngeal cancers is also noted. It is also shown that antibody to herpes simplex virus type II is found in 90% of patients with cervical carcinoma, while both previous herpes zoster and herpes simplex virus type I infection are related to the subsequent development of skin cancer by anecdotal evidence. Thus the lymphoproliferative tumors, carcinoma of

the skin, and carcinoma of the cervix are all previously associated with herpesvirus infections whose persistence in the transplant patient is indicated by frequent clinical exacerbations or constant shedding. It is suggested that (oncogenic) herpesviruses rest in lymphocytes and/or in neural tissue during latency, and are reactivated by the chronic antigenic stimulation of the graft in the immunosuppressed patient. While the development of vaccines to prevent herpesvirus infections in such patients is suggested, the development of substances to prevent reactivation of the viruses is considered more important.

3808 ENHANCEMENT OF MOLONEY SARCOMA VIRUS-INDUCED TUMOR GROWTH BY CONCANAVALIN A. (Eng.) Davis, S. (Natl. Cancer Inst., Bethesda, Md.); Redmon, L. W.; Pearson, G. R. *Immunol. Commun.* 4(1): 29-37; 1975.

In an attempt to further delineate the role of the T cell in the immune response to Moloney sarcoma virus (MSV) *in vivo*, the immunosuppressive effects of concanavalin A (Con A) on tumor growth was studied in mice inoculated with 10^6 focus forming units/ml MSV. Adult male Balb/c mice were injected ip with Con A (100 μg) three times weekly, beginning either on day zero relative to virus inoculation or when the tumors reached 6 mm in size. In mice treated with Con A commensurate with the appearance of 6 mm tumors, a significantly higher percentage of progressively growing tumors (79%) than in the mice treated only with virus (39%) was observed. Treatment with Con A on day zero relative to MSV inoculation had no significant effect. Antibody production as measured by indirect membrane fluorescence was not affected by Con A. Because *in vivo*-administered Con A is known to have a specific suppressive effect on T lymphocytes, it is suggested that the primary immunologic response to MSV antigens is a function of T cells.

3809 STUDIES ON THE BUDDING PROCESS OF A TEMPERATURE-SENSITIVE MUTANT OF MURINE LEUKEMIA VIRUS WITH A SCANNING ELECTRON MICROSCOPE. (Eng.) Wong, P. K. Y. (Sch. Basic Medical Science, Univ. Illinois, Urbana, Ill. 61801); MacLeod, R. *J. Virol.* 16(2):434-442; 1975.

The scanning electron microscope was used to study the budding process of the wild-type Moloney murine leukemia virus and one of its temperature-sensitive mutants, designated ts 3. A considerably larger number of budding particles was observed on TB cells infected with ts 3 at the nonpermissive temperature (39 C) than at the permissive temperature (34 C). No apparent difference was noted between the number of particles on ts 3-infected cells at 34 C and wild-type-infected cells at 34 or 39 C. Virions were detected at the cell membrane of ts 3-infected cells at 39 C as early as eight hours postinfection. Virion density increased progressively up to 48 hr, after which no increase was observed. An average of 1,600 virus particles was observed at the cell surface at the peak of virus production. The distribution of these on the cell membrane appeared to be random. The maximum proportion of the cell surface occupied by the viral particles did not exceed 10%. After temperature shift from 39 to 34 C, approximately 90% of the particles had dissociated from the cell membrane within one hour.

3810 SARCOMA IN A HAMSTER INOCULATED WITH BK VIRUS, A HUMAN PAPOVAVIRUS. (Eng.) Shah, K. V. (Johns Hopkins Univ., Sch. Hyg. Public Health, Baltimore, Md.); Daniel, R. W.; Strandberg, J. D. *J. Natl. Cancer Inst.* 54(4):945-950; 1975.

A sarcoma occurring in one hamster inoculated with a human papovavirus, BK virus (BKV), is described. Outbred Syrian hamsters LAK:LGV (SYR) were used, with half being neonatally thymectomized. They were inoculated either within 24 hr of birth with 0.1 ml (6.5 $\log_{10}$ units) virus sc, or at five weeks of age with 0.5 ml (8.8 $\log_{10}$ units) concentrated virus iv; the latter mice were examined every two weeks for lymph gland tumors. Tumors appeared, depending on the route of inoculum, but only one was detected after one year. The tumor was maintained by transfer *in vivo* or by passage *in vitro*. The cells of the third passage (CC-3) from the original tumor were reacted with 52 sera from hamsters with large, second- to fifth-passage tumors. Only four of these sera stained the tumor in indirect immunofluorescence tests. The sera reactive to the CC-3 tumor cells were also reactive to BKV-infected WI-38 cells, with 63 sera being reactive. There was a high correlation between readings of the sera to BKV and simian virus 40 (SV40)-infected cells. Reactivity of the tumor cells was increased by reducing fixation time to five minutes and storage at -70 C. There was considerable cross-reactivity between the T antigens of BKV and SV40 viruses. In repeated immunofluorescence tests with BKV-immune rabbit sera, tumor cells were negative for BKV virion antigens. BKV was not rescued by fusion of CC and CS tumor cell lines with VERO and WI-38 cells. BKV immunization also failed to protect against challenge with sarcoma virus or SV40 tumor cells. These data indicate that at least part of the BKV genome is present in these tumor cells, and that the integrated BKV genome is defective.

3811 SEROLOGICAL ANALYSIS OF AN ONCORNAVIRUS (PMF VIRUS) DETECTED IN MALIGNANT PERMANENT HUMAN CELL LINES. *(Eng.)* Micheel, B. (Central Inst. for Cancer Res. of the Acad. Sciences of the GDR, Dept. Virology and Experimental and Clinical Immunology, 1115 Berlin-Buch, East Germany); Papsdorf, G.; Wunderlich, V.; Niezabitowski, A.; Widmaier, R.; Bender, E.; Graffi, A. *Acta Biol. Med. Ger.* 34(4):K39-K45; 1975.

A serological analysis of the PMF virus detected in a permanent malignant human cell line was conducted by means of an immunodiffusion test using antisera against different known oncornaviruses. Most experiments were performed with antigen preparations from permanently cultivated ovarian carcinoma cells (line Tu 197) infected with PMF virus. The virus showed a positive reaction with antisera against Mason Pfizer monkey virus (MPMV).

No cross-reactivity was demonstrated with murine virus, rat leukemia virus, hamster leukemia virus, feline leukemia virus, simian sarcoma virus, or mouse mammary tumor virus. The reaction with antisera to MPMV was specific for PMF viral antigens since no positive reaction was obtained with soluble extracts or gradient purified material from non-infected Tu 197 cells. The cross-reactive antigens of PMF virus and MPMV are evidence for the human origin of PMF virus.

3812 CHICK MUSCLE IN TISSUE CULTURE: THE UBIQUITY OF VIRAL INFECTION. (Eng.)
Askanas, V. (Inst. Rehabilitation Medicine, New York Univ. Medical Center, N.Y.); Engel, W. K. *Acta Neuropathol. (Berl.)* 32(4):271-279; 1975.

The presence of viral C-particles and avian leukosis/sarcoma envelope antigen was investigated in chick muscle tissue culture. Trypsinized breast muscle of chick embryos from "normal" egg from a commercial flock uncertified as to leucosis status were cultured from 3-5 wk. The cultured cells were examined by electron microscopy. Complement fixation tests for avian leukosis virus envelope antigens (COFAL) of groups A, B and C were performed on the extracts of the cell cultures. To some cultures 0.1-0.5 mM dinitrophenol pulses were given one hour daily for the last ten days. C-particles, presumably of avian leukosis virus and COFAL positivity were present in all of the muscle cultures. The number of virus particles was enhanced in the dinitrophenol-treated cultures. Dinitrophenol treatment increased up to 8-fold the COFAL titers. Extracts of embryos before culturing were COFAL negative. C-particles of about 600-750 A in diameter were present in multinucleated cross-striated fibers of all the muscle cultures. Singly or in small groups they were always enclosed by a single membrane within the fibers. In a number of areas, C-particles were in t-tubule-like invaginations, which were possible intracellular viaducts of infection or dissemination. C-particles were never seen budding from the sarcolemma of muscle fibers. The abundant lace-like membranous proliferations, probably of t-tubules, usually had C-particles adjacent to or within them. The enhanced production of C-particles and viral envelope antigen by dinitrophenol raises the questions of whether some virus genome was in the mitochondria and whether part of mitochondrial damage was through activated mitochondrial virus.
mobility than gp85 was formed. The labeling properties of this component suggested that it was a carbohydrate-deficient form of gp85. The biochemical basis for the glucosamine-related inhibition of virus synthesis is unknown.

3813 SYNTHESIS OF VIRAL PROTEINS BY THE AVIAN MYELOBLASTOSIS VIRAL CORE COMPONENT.
(Eng.) Mendelson, I. S. (Univ. Illinois Medical Center, Chicago, Ill. 60680). *Biochim. Biophys. Acta* 407(4):442-448; 1975.

The capacity of isolated avian myeloblastosis viral (AMV) core component to synthesize AMV proteins *in vitro* was tested. Viral core component was isolated from the disrupted virus and was purified by discontinuous sucrose gradient centrifugation. The *in vitro* protein was measured by incorporation of ^{3}H-leucine in the presence of ATP, CTP, GTP, phosphocreatine, creatine phosphokinase, 19 unlabeled amino acids, and known units of viral core. The reaction was incubated and spotted on Whatman filters and dropped into cold trichloroacetic acid. After boiling and processing the samples were counted in a liquid scintillation counter. The *in vitro* products were incubated with ribonuclease. The solubilized proteins were immunoprecipitated by a double antibody technique, and were analyzed by polyacrylamide gel electrophoresis and by guanidine hydrochloride agarose column chromatography. The uptake of ^{3}H-leucine by the AMV core component was linear for 120 min. The incorporation of ^{3}H-leucine was proportional to the concentration of viral cores. Puromycin and aurintricarboxylic acid inhibited the *in vitro* reaction. The *in vitro*-synthesized proteins coelectrophoresed and cochromatographed with known proteins, and were immunoprecipitated by total and monospecific antibodies to known AMV proteins. The authors conclude that the protein synthesizing system may be an integral part of the structure of the AMV core and may serve to translate *in vivo* the viral genome.

3814 INHIBITION OF ROUS SARCOMA VIRUS BY α-AMANITIN: POSSIBLE ROLE OF CELL DNA-DEPENDENT RNA POLYMERASE FORM II. (Eng.) Dinowitz, M. (Arizona Medical Center, Univ. Arizona, Tucson, Ariz. 85724). *Virology* 66(1):1-9; 1975.

The effect of α-amanitin, an inhibitor of the cell nuclear form II DNA-dependent RNA polymerase, on Rous sarcoma virus (RSV) synthesis in RSV-transformed chick embryo cells was examined. Utilizing incorporation of [^{3}H]uridine into virions as a sensitive measure of RSV synthesis and of inhibition of synthesis by α-amanitin, inhibition of virus production could be detected within two hours after addition of the toxin to the cells. The dose response of transformed cells showed about a 15% reduction in virus production at levels of 1-3 μg/ml α-amanitin within three hours. Analysis of the appearance of newly labeled [^{3}H]RNA onto polyribosomes showed early partial inhibition by the toxin at a rate similar to the rate of inhibition of RSV synthesis. Little if any inhibition of ribosomal RNA (rRNA), the product of the nucleolar form I DNA-dependent RNA polymerase, was detectable until several hours after the initial inhibition of RSV was observed. These data indicate that RSV requires the form II polymerase, or an enzyme with a similar sensitivity to α-amanitin, for replication.

3815 FURTHER EVIDENCE FOR THE EXISTENCE OF A VIRAL ENVELOPE PROTEIN DEFECT IN THE BRYAN HIGH-TITER STRAIN OF ROUS SARCOMA VIRUS. (Eng.)
Ogura, H. (Institut fur Virologie Fachbereich Humanmedizin, Justus-Liebig-Universitat, 6300 Giessen, West Germany); Friis, R. *J. Virol.* 16(2):443-446; 1975.

The hypothesis that Bryan high-titer Rous sarcoma

virus (BH RSV) is unable to make functional viral envelope proteins was further investigated. BH RSV was observed with the electron microscope following freeze-drying. Progeny made in the absence of a helper virus lacked visible surface projections or spikes. Phenotypic mixing experiments employing BH RSV and a thermolabile mutant of vesicular stomatitis virus, *tl* 17, yielded no evidence of pseudotype formation. Since *tl* 17 is known to be defective for an envelope glycoprotein, the lack of successful phenotypic mixing with BH RSV is consistent with the observed absence of viral spikes.

3816 *IN VITRO* TRANSCRIPTION OF DNA FROM THE 70S RNA OF ROUS SARCOMA VIRUS: IDENTIFICATION AND CHARACTERIZATION OF VARIOUS SIZE CLASSES OF DNA TRANSCRIPTS. (Eng.) Collett, M. S. (Univ. Minnesota Medical Sch., Minneapolis, Minn. 55455); Faras, A. J. *J. Virol.* 16(5):1220-1228; 1975.

Data indicating that the RNA-directed DNA polymerase of Rous sarcoma virus (RSV) is capable of transcribing large regions of RSV 70S RNA into DNA is presented. The synthesis of DNA by detergent-disrupted virions of the Schmidt-Ruppin and B77 strains of RSV was performed using standard reaction mixtures containing rate-limiting concentrations of one of the deoxynucleoside triphosphates or equimolar concentrations of deoxynucleoside triphosphate precursors. The DNA products were analyzed by polyacrylamide gel electrophoresis, alkaline sucrose sedimentation, and nucleic acid hybridization. Although the bulk (75%) of the DNA synthesized under rate-limiting concentrations of precursor migrated in the range of 4-7S RNA markers in the polyacrylamide gels, a portion of the DNA migrated between the 7S and 18S markers. However, less than 40% of the DNA transcripts synthesized in the presence of equimolar concentrations of deoxynucleoside triphosphates were found in the regions containing the 4S and 7S markers. Larger DNA chains, ranging between 1,500 and 4,500 nucleotides in length, represented less than 5% of the total DNA product synthesized in the presence of rate-limiting concentrations of TTP. In the presence of equimolar concentrations of precursors, however, about 20% of the total DNA product exhibited a sedimentation coefficient of 10S in alkaline sucrose gradients. Nucleic acid hybridization studies confirmed the length and genetic complexity of the larger DNA transcripts. The identification of large DNA chains in the DNA product synthesized *in vitro* by the RSV RNA-directed DNA polymerase provides an explanation for the paradox existing between the limited number of primer sites per 70S RNA genome, the small size of the bulk of the DNA product, and the extent of the RSV genome represented by the DNA product.

3817 THE ROLE OF THE *tvb* LOCUS IN GENETIC RESISTANCE TO RSV(RAV-0). (Eng.) Crittenden, L. B. (ARS Animal Physiology and Genetics Inst., Beltsville, Md. 20705). Motta, J. V. *Virology* 67(2):327-334; 1975.

To identify the loci controlling recessive resistance to RSV(RAV-0), a subgroup E avian sarcoma virus, genetic susceptibility to this virus and to RSV(RAV-2), a subgroup B sarcoma virus, was studied in two inbred chicken lines (RPRL line 100, which is maintained by repeated backcrossing of males to RPRL line 7 females, and Reaseheath line C). Reciprocal F_1 crosses of lines 7 and C were made, and female progeny resulting from these matings were backcrossed to line 7 and line C males. Line 100 males were crossed with line C females, and the F_1 female progeny were mated with line 7 or C. Chorioallantoic membranes of eggs resulting from these crosses were tested for pack formation after virus inoculation, and R_1 erythrocyte antigen was assayed in the RBC of adults and embryos. Susceptibility in the progeny of the crosses between lines 7 and C corresponded to the expectation of the single-locus hypothesis; this is based on the belief that susceptibility to subgroup E is controlled by a single tumor virus locus *tvb* but that an allele in line C codes for susceptibility to subgroup B and for resistance to subgroup E. Susceptibility to RSV(RAV-2) among the results of these matings indicated that line C carried recessive genes that incompletely repressed susceptibility to subgroup B virus. Similarly, crosses of lines 100, C, and 7 supported the single-locus hypothesis with respect to susceptibility to RSV(RAV-0) and RSV(RAV-2). Furthermore, a complete association of RSV(RAV-0) susceptibility and the R_1 antigen was found when R_1-positive 100 x C dams were crossed with either line 7 or line C males. Thus, the data completely support the hypothesis that a single locus controls recessive resistance to subgroup B and E viruses; no evidence for an independent *tve* locus was obtained. The data also support the hypothesis that the *tvb* locus had multiple alleles, one of which is associated with the R_1 erythrocyte antigen.

3818 VIRAL GLYCOPROTEIN SYNTHESIS UNDER CONDITIONS OF GLUCOSAMINE BLOCK IN CELLS TRANSFORMED BY AVIAN SARCOMA VIRUSES. (Eng.) Lewandowski, L. J. (Wistar Inst. Anatomy and Biology, 36th & Spruce Sts., Phila., Pa. 19104); Smith, R. E.; Bolognesi, D. P.; Halpern, M. S. *Virology* 66(2): 347-355; 1975.

The synthesis of the viral glycoprotein gp85 in avian sarcoma virus strain B77-transformed chick embryo cells cultured under conditions of glucosamine block was studied. Confluent secondary cultures of noninfected or transformed cells were incubated for six hours in medium containing 20 μM/ml glucosamine-HCl. The medium was then removed, and the cells were incubated for ten hours in medium 90% deficient in amino acids and containing 50 μCi/ml of ^{3}H-labeled amino acid mixture or [^{3}H]fucose. For pulse labeling, the cells were cultured for six hours with or without glucosamine, after which the medium was replaced with Hank's balanced salt solution (with or without glucosamine) containing 100 μCi/ml of ^{3}H-labeled amino acid. Rabbit anti-gp85 and goat anti-rabbit γ-globulin serum were utilized for the indirect immune precipitation of intracellular gp85. The immune precipitates were analyzed by sodium dodecyl sulfate (SDS)-polyacrylamide-gel electrophore-

sis. No detectable virus was found in the supernatant fluids of the glucosamine-treated cultures, but removal of the glucosamine resulted in the restoration of virus synthesis to nearly 90% of the level seen in untreated control cultures. The observed inhibition was not due to a near total shut-off of host protein synthesis under conditions of glucosamine block. When gp85 synthesis was examined in the presence and absence of glucosamine, significant quantities of amino acid-labeled gp85 were found in the lysate of the untreated transformed culture, but not in the lysate of the glucosamine-treated culture. Pulse-labeling experiments indicated that these results were not due to rapid catabolism following normal viral glycoprotein synthesis; rather, it appeared that the lack of gp85 accumulation was due to a decreased rate of viral glycoprotein synthesis in the presence of glucosamine. Long-term labeling with [^{3}H]fucose showed that although no gp85 was formed in the presence of glucosamine, an intracellular component that was recognized by anti-gp85 serum but migrated in SDS-polyacrylamide gels with a greater

3819 MAPPING THE TRANSCRIPTION SITE OF THE SV40-SPECIFIC LATE 16 S mRNA. (Eng.) May, E. (Unite de Biophysique, Institut de Recherches Scientifiques sur le Cancer, BP No. 8, 94 800-Villejuif, France); Kopecka, H.; May, P. *Nucleic Acids Res.* 2(10):1995-2005; 1975.

Polysomal RNA was purified from simian virus 40 (SV40)-lytically infected cells, and 19S and 16S RNA classes were separated and hybridized with simian virus 40 DNA and its *Hind*-fragments. Viral lysates were obtained by infection of CV1 monkey kidney cells with dilute viral preparations (0.005 plaque forming units (PFU)/cell). [^{14}C]-Labeled viral lysates used for the preparation of *Hind*-fragments of SV40 DNA were obtained by labelling infected cultures with [^{14}C] methyl thymidine from the seventh to the tenth day after infection. Late SV40-specific polysomal RNA was obtained by infecting CV1 cultures with 100-200 PFU/cell before the cells became confluent at 24 hr after seeding. The virus was adsorbed for one hour; 24 hr after infection, the cultures were labeled with [^{3}H]-5-uridine for six hours and the nuclear and cytoplasmic fractions were separated by centrifugation. The postmitochondrial supernatant was centrifuged through a sucrose double layer to give a pellet that was more than 80% polyribosomes. The pellet was resuspended and fractionated through a sucrose density gradient to give two classes with a sedimentation coefficient of about 19 and 16S. When the fractions were pooled and resedimented in a sucrose gradient, the radioactive hybridizable RNA sedimented as a uniform band with a sedimentation coefficient of 19 S and 16 S. The 19 S and 16 S preparations contained, respectively, 10% and 16% of radioactive RNA hybridizable with whole SV40 DNA as compared to the total acid precipitable radioactivity present in these preparations. The 19S and 16S preparations were divided into several portions and hybridized with whole SV40 DNA and with the *Hind* fragments. The results are consistent with the theory that the 19S SV40 messenger RNA preparation contains a major constituent transcribed from all or the major part of the late region of the viral genome plus 10-20% of the early SV40 19S messenger RNA transcribed from the early region of the viral genome. The results also suggest that the SV40 16S messenger RNA preparation contains a late SV40 16S RNA species transcribed from a region including the *Hind*-fragments K,F,J, and G and that this region is located between 0.945 and 0.175 map units.

3820 RNAs OF SIMIAN VIRUS 40 IN PRODUCTIVELY INFECTED MONKEY CELLS: KINETICS OF FORMATION AND DECAY IN ENUCLEATE CELLS. (Eng.) Aloni, Y. (Weizmann Inst. of Science, Rehovot, Israel); Shani, M.; Reuveni, Y. *Proc. Natl. Acad. Sci. USA* 72(7):2587-2591; 1975.

The usefulness of cytochalasin B enucleate cells for the study of metabolism of cytoplasmic messenger RNA (mRNA) and for determining its half-life in animal cells was investigated. BSC-1 monkey cell cultures were infected with plaque-purified simian virus 40 (SV40, strain 777); the RNA was labeled with [^{3}H]uridine 3-48 hr after infection. After infection, the cells were enucleated by exposure to cytochalasin B (10 μg/ml) in Eagle's medium supplemented with amino acids, vitamins, and 2% calf serum. The ^{3}H-labeled RNA was extracted from the cells and digested with 50 μg/ml of DNase I, after which the digest was extracted with sodium dodecyl sulfate/phenol and fractionated on sucrose gradients. RNA-DNA hybridization was used to distinguish the labeled SV40 RNA from the background of cellular RNA. About 80% of the virus-specific RNA in the cells was distributed with several reproducible peaks between the 28S and 18S ribosomal RNA markers on the sucrose gradients. The molecules present in the first recognizable viral RNA peak (26S) appeared to be the primary viral RNA transcripts, while the RNA molecules present in the third (19S) peak were the final products of the processing of the viral RNA in the nucleus. The major viral component in the cytoplasm was 16S RNA, but it was not detected in the nucleus. The 19S species was also found in the cytoplasm, and the change in the proportion of the 19S and 16S RNAs took place after they entered the cytoplasm. The decay rate of the 19S component approximated first-order kinetics, with a mean half-life of about three hours. The decay curve for the 16S component, on the other hand, could be divided into two periods: up to 5-6 hr after infection, there was a slight increase in the radioactivity incorporated into the 16S RNA; after that, decay proceeded exponentially with a half-life of about six hours. The results indicate a precursor-product relationship between the 19S and 16S species.

3821 TEMPERATURE DEPENDENCE OF STRAND SEPARATION OF THE DNA MOLECULES CONTAINING INTEGRATED SV40 DNA IN TRANSFORMED CELLS. (Eng.) Fried, A. H. (Institut fur Virusforschung, Deutsches Krebsforschungszentrum, 69 Heidelberg, West Germany). *Nucleic Acids Res.* 2(9):1591-1608; 1975.

A procedure was established for the analysis of

temperature dependence in DNA molecules which contain the integrated simian virus 40 (SV40) DNA in transformed mouse cells. The size of the DNA molecules isolated from SVT2 cells was measured after their exposure to different temperatures by employing sedimentation analysis at alkaline pH. The T_m of linear SV40 DNA was then measured using SV40 DNA III molecules (generated using the R_1 restriction endonuclease) and SV40 DNA II molecules (generated using pancreatic DNase). The melting curves of these populations were determined using an RNA-DNA hybridization assay specific for single-stranded DNA, a nitrocellulose filter binding assay (which is also specific for single-stranded DNA), and by assaying for the amount of single-stranded DNA with the S_1 endonuclease after heating and cooling the DNA. Finally, the melting curves of the SV40-cellular DNA molecules from three cloned transformed mouse cell lines (SVT2, 11A8, and SV3T3-47) were measured. The size of the cellular DNA molecules was about 17 times that of a unit length of the SV40 DNA molecule even when the DNA was heated to 65 C for ten minutes. The RNA-DNA hybridization assay gave the same T_m for a unit length of SV40 DNA molecule as the S_1 nuclease assay and the nitrocellulose filter binding assay. Also, the width of the transition in the melting curve was of comparable sharpness, not more than two degrees, using all three assays. The T_m of almost all of the SV40-cellular DNA molecules was greater than that of unit length SV40 DNA. Combining the results from all three transformed cell lines, SV40-cellular DNA molecules that underwent complete strand separation at 55-68 C were found. Thus, SV40-cellular DNA molecules that undergo complete strand separation with a range of 1-2 degrees would represent a homogenous group of molecules with respect to those cellular base sequences which determine the T_m of the molecules. In the 11A8 cell line, about 40% of the integrated SV40 DNA could be accounted for by such a homogenous group. The results indicate that RNA-DNA hybridization is a reliable method for deciding whether or not a molecule containing SV40 base sequences has undergone complete strand separation.

3822 INITIATION AND MAINTENANCE OF CELL TRANSFORMATION BY SIMIAN VIRUS 40: A VIRAL GENETIC PROPERTY. (Eng.) Kimura, G. (Tottori Univ. Sch. Med., Yonago 683, Japan); Itagaki, A. *Proc. Natl. Acad. Sci. USA* 72(2):673-677; 1975.

The role of simian virus 40 (SV40) genes in biological phenomena induced in cells after infection and transformation by this virus was studied. The transforming ability in 10% serum medium of the temperature-sensitive mutants of SV40 in the complementation group III (*ts*6-40 type mutants) was greatly reduced when infected rat 3Y1 cells were incubated at the restrictive temperature of 40 C or incubated first at 40 C for three days and then shifted to the permissive temperature of 33 C. Transformation did occur efficiently after incubation at 33 C or after an initial incubation at 33 C for five days followed by a shift to 40 C. When growth properties of 3Y1 cells transformed at 33 C by the group III mutants were examined at 40 C, several aspects of the transformed state were rendered temperature-sensitive. These aspects were the ability of cells to grow in low serum (1.5%) medium and to make colonies, in 10% serum medium, on monolayers of untransformed 3Y1 cells and in soft agar. It is concluded that a simian virus 40 gene (cistron III) controls the initiation, as well as at least some aspects of the maintenance, of transformation and that the initiation reaction is a more heat-labile event than the maintenance reaction(s) under the experimental conditions.

3823 CIRCULAR DNA FROM HETEROKARYONS OF SV40-TRANSFORMED MOUSE AND AFRICAN GREEN MONKEY CELLS. *(Eng.)* Yoshiike, K. (Natl. Inst. Health, 2-10-35 Kamiosaki, Shinagawa-ku, Tokyo 141, Japan); Watanabe, S.; Suzuki, K.; Uchida, S. *Jpn. J. Microbiol.* 19(3):237-240; 1975.

In an attempt to explore a method for the study of simian virus 40 (SV40) genome excision, closed circular DNA was extracted from heterokaryon cultures of SV40-transformed mouse and susceptible monkey cells and its length determined by electron microscopy. Dish cultures and coverslip cultures were prepared from incubation mixtures of African green monkey kidney (GMK) cells, transformed mouse 3T3-L or 3T3-M cells, and UV-inactivated Sendai virus. After 72 hr of cultivation, the coverslips were stained with fluorescent antibodies and circular DNA was extracted from the dish cultures. The circular DNA molecules from the heterokaryon cultures appeared to be heterogeneous and ranged in size from 1.0-3.0 μm. The molecules constituting the largest proportion of the population had a length similar to that of the viral genome. The viral DNA from transformed 3T3-M cells, which is believed to have been transformed by defective SV40, was approximately 12% shorter than that from 3T3-L cells containing the complete genome. V- and T-antigen positive cells were found in the heterokaryon cultures of GMK cells and transformed 3T3-L cells, but cultures of GMK and transformed 3T3-M cells contained only T-antigen positive cells. The method used in this study, if applied to various transformed cell lines including those transformed by defective deletion mutants, may provide information about the excision of the SV40 genome.

3824 DNA REPLICATION IN SYNCHRONIZED CULTURED MAMMALIAN CELLS. V. THE TEMPORAL ORDER OF SYNTHESIS OF COMPONENT α DNA DURING MONKEY DNA SYNTHESIS INDUCED BY SV40 VIRUS. (Eng.) Parker, R. J. (Albert Einstein Coll. Medicine, 1300 Morris Park Ave., Bronx, N. Y. 10461); Tobia, A. M.; Baum, S. G.; Schildkraut*, C. L. *Virology* 66(1):82-93; 1975.

Purified simian virus 40 (SV40) was used to induce host DNA replication in contact-inhibited monolayer cultures of African green monkey kidney cells. Approximately 20% of the nuclear DNA of these cells is the simple sequence, component α DNA. At the beginning of DNA synthesis induced by SV40 viral infection, the average ratio of the specific radioactivity of component α DNA to that of bulk DNA was 0.18. Similar low specific activity ratios

were observed early during the DNA synthetic period following the trypsin release of monkey cells from contact inhibition. These results indicate that when host DNA replication is induced by SV40 viral infection, component α DNA synthesis does not shift to precede the replication of bulk DNA.

3825 EVOLUTIONARY VARIANTS OF SIMIAN VIRUS 40: CLONED SUBSTITUTED VARIANTS CONTAINING MULTIPLE INITIATION SITES FOR DNA REPLICATION. (Eng.) Lee, T. N. H. (The Johns Hopkins Univ. Sch. Medicine, Baltimore, Md. 21205); Brockman, W. W.; Nathans, D. *Virology* 66(1):53-69; 1975.

Two cloned evolutionary variants of simian virus 40 (SV40) containing substitutions of cellular DNA were characterized by restriction endonuclease analysis, electron microscopic heteroduplex mapping, and DNA-DNA hybridization. Each variant genome was made up of a small, tandemly repeated segment of DNA consisting of cellular DNA and that portion of the SV40 genome containing the initiation signal for viral DNA replication. Cellular DNA sequences were different in the two variants, indicating that recombination between cell DNA and SV40-DNA can occur at more than one site. However, one end of the SV40 segment (0.68 SV40 map-units) was the same in each variant. The data suggest that substituted variants arise by integration of SV40-DNA into cellular DNA followed by excision of a small substituted genome which is subsequently amplified to a size compatible with encapsidation; the presence of multiple initiation signals in each molecule results in selective replication.

3826 EVOLUTIONARY VARIANTS OF SIMIAN VIRUS 40: CHARACTERIZATION OF CLONED COMPLEMENTING VARIANTS. (Eng.) Brockman, W. W. (The Johns Hopkins Univ. Sch. Medicine, Baltimore, Md. 21205); Gutai, M. W.; Nathans, D. *Virology* 66(1):36-52; 1975.

Three evolutionary variants of simian virus 40 (SV40), cloned by complementation with temperature-sensitive SV40 mutants, were mapped by restriction endonuclease analysis and by electron microscopic heteroduplex mapping. One of the variants contains a deletion of most of the "late" region of the genome, and the other two contain nonidentical deletions within the "early" region. Each of the variants has a distinctive duplication of a DNA segment which includes the initiation site for DNA replication. Based on the physical maps of these genomes, a recombinational mechanism was suggested for the generation of variants; once generated, encapsidable molecules with duplications of the replication initiation site would have a selective growth advantage. One variant contains one of its two initiation sites close to the site where SV40 DNA replication normally terminates. In this variant, however, replication appears to terminate 180° from the initiation point. Therefore, unlike initiation, termination of SV40 DNA replication is probably not sequence specific.

3827 IDENTIFICATION OF SELF-COMPLEMENTARY VIRUS-SPECIFIC RIBONUCLEIC ACID IN CHICK KIDNEY CELLS INFECTED WITH CHICKEN EMBRYO LETHAL ORPHAN VIRUS. (Eng.) May, J. T. (John Curtin Sch. Med. Res., Australian Natl. Univ., Canberra); Robinson, A. J. *J. Gen. Virol.* 26(2):209-213; 1975.

The effect of exposure to a pulse of uridine on self-annealing and self-complementary RNA was investigated. RNA was extracted from primary chicken embryo kidney cells infected with chicken embryo lethal orphan virus and exposed to a pulse of [5-^{3}H]-uridine late in infection (i.e., after 19 hr). The cells were lysed, and phenol was extracted without using chloroform. Pulse-labeled RNA from the virus infected cells was 2.5% resistant to pancreatic ribonuclease digestion, as compared to a 1.4% resistance of the uninfected cells. Upon self-annealing, the amount of ribonuclease-resistant RNA increased in both the infected and uninfected cell extracts (to levels of 4.5% and 2.0%, respectively). Upon chromatography on a Sephadex G-100 column, labeled RNA eluted with the void volume in both the infected and uninfected cell RNA; the virus-infected cell RNA contained a 3-fold higher proportion of the loaded sample in the void volume. Experiments done to establish the double-stranded nature of the RNA eluting in the void volume illustrated both the melting profile and cesium sulfate density characteristics of double-stranded RNA; once heated, the RNA behaved like single-stranded RNA. Furthermore, the ribonuclease-resistant RNA extracted from both uninfected and infected RNA had identical sedimentation values of 8S in sucrose. About 50% of the virus-infected RNA was found to anneal to chick embryo lethal orphan DNA, while only 1% of uninfected RNA was bound; similar values were obtained in four separate preparations. Of the RNA that hybridized to the chick embryo lethal orphan DNA, about equal amounts bound to the heavy and light strands. The experiments indicate that self-complementary virus-specific RNA, forming double-stranded RNA under self-annealing conditions, is produced late in the chick embryo lethal orphan virus infection of chick embryo kidney cells; this represents 0.45% of the RNA synthesized during a one-hour period late in infection.

3828 ELECTROPHORETIC MOBILITIES OF RNA TUMOR VIRUSES. STUDIES BY DOPPLER-SHIFTED LIGHT SCATTERING SPECTROSCOPY. (Eng.) Rimai, L. (Scientific Res. Staff, Ford Motor Co., Dearborn, Mich. 48121); Salmeen, I.; Hart, D.; Liebes, L.; Rich, M. A.; McCormick, J. J. *Biochemistry* 14(21): 4621-4627; 1975.

The electrophoretic mobilities, at several pH values, of purified avian myeloblastosis (AMV), murine leukemia (MuLV), murine mammary tumor (MuMTV), and feline leukemia (FeLV) viruses were measured by laser beat frequency light scattering spectroscopy. The mobilities of these viruses are similar at pH $\geq$ 7 (-2.7 to -3.2 x 10^{-4} cm/sec V/cm). The isoelectric points of MuLV and AMV are apparently less than pH 3, whereas for FeLV the data suggest an isoelectric point between 3 and 5. By using a Debye-Huckel model to describe the interactions between electrolytes and virus, it was shown that the values for the mobility of MuMTV obtained in low ionic strength buffer (0.005) are consistent with the values previously obtained in high ionic strength buffer (0.10). This model

was also used to calculate the surface charge densities of the virions. A comparison between virus and RBC data at pH > 7 indicates that in terms of the surface charge density, the envelope of the RNA tumor viruses is not very different from the RBC membrane. It is suggested that the mobility measured at pH $\geq$ 7 may be a general characteristic of RNA tumor viruses and, in combination with the diffusion constant and the bouyant density, may be useful in assaying the presence of such viruses.

3829 INTRACELLULAR SYNTHESIS OF MOUSE MAMMARY TUMOR VIRUS POLYPEPTIDES: INDICATION OF A PRECURSOR GLYCOPROTEIN. (Eng.) Dickson, C. (Cancer Res. Lab., Univ. California, Berkeley, Calif. 94720); Puma, J. P.; Nandi, S. *J. Virol.* 16(2):250-258; 1975.

Mouse mammary tumor virus polypeptides were detected in the cytoplasm of mouse mammary tumor cell cultures (BALB/cfC3HCrgl spontaneous mammary adenocarcinomas) using immunological precipitation techniques. The anti-mouse mammary tumor virus serum precipitated the major virion glycoproteins gp49 and gp37.5/33.5 and a viral-related nonvirion glycoprotein of 76,000 daltons. Subcellular fractionation studies revealed that the cell-associated virion glycoproteins were present in the membrane fraction. Pulse-chase experiments indicated that a viral-related nonvirion glycoprotein of 76,000 daltons may be a precursor to one or more of the virion glycoproteins.

3830 C-TYPE VIRUS ANTIGENS DETECTED BY IMMUNOFLUORESCENCE IN HUMAN BONE TUMOUR CULTURES. (Eng.) Zurcher, C. (Inst. for Experimental Gerontology TNO, Rijswijk, Z.H., The Netherlands); Brinkhof, J.; Bentvelzen, P.; de Man, J. C. H. *Nature* 254(5499):457-459; 1975.

Indirect immunofluorescence was used to detect antigens which have determinants in common with the Rauscher murine and simian leukemia viruses (RLV and SLV) in human bone tumor cultures. Rat anti-RLV and guinea pig anti-SLV did not react with uninfected animal cell lines, but gave a very strong reaction with cultures infected with the viruses to which the antisera were directed; there was a significant cross reaction between RLV and SLV. The bovine leukosis virus (BoLV) did not show a cross reaction with either RLV or SLV. One of six rat antisera to RLV reacted with several human bone tumor cultures and a woolly monkey virus antiserum also gave a positive reaction with several human bone tumor cultures. Rat anti-RLV serum reacted with a SLV-producing culture but not with any of the human bone tumor cultures, and tumor lines which reacted with anti-RLV or anti-SLV did not react with a goat serum which specifically reacts with the BoLV. The fluorescence with anti-RLV and anti-SLV varied per passage, especially early passages being highly positive. Absorption of the antisera with RLV isolated from the plasma of leukemic mice or with murine mammary tumor virus markedly reduced the reaction in the immunofluorescence assay on RLV-infected cells and completely blocked the reaction with human tumors; similar results were obtained after *in vivo* absorption and after absorption of the antiserum to SLV with SLV. Control absorptions only slightly diminished the reaction in both systems. The results suggest that cultures from human bone tumors harbor a viral entity that occasionally produces antigens which have determinants in common with known animal C-type oncornaviruses.

3831 C-TYPE VIRUS PARTICLES IN PLACENTA OF NORMAL HEALTHY SPRAGUE-DAWLEY RATS. (Eng.) Gross, L. (Veterans Admin. Hosp., Bronx, N.Y. 10468); Schidlovsky, G.; Feldman, D.; Dreyfuss, Y.; Moore, L. A. *Proc. Natl. Acad. Sci. USA* 72(8): 3240-3244; 1975.

Placentas from four young, healthy Sprague-Dawley rats were examined with the electron microscope for the presence of C-type virus particles. These particles were found in two specimens. One specimen contained virus particles budding from the plasma membrane of cells in the junctional zone of the placenta, i.e., the region where the fetal and maternal cell layers meet. In the other placenta, immature and mature C-type virus particles were observed among cell debris in the junctional region. These findings place the rat placenta in the same group as those of several other species, such as rhesus, baboon, and marmoset monkeys, as well as humans, in which C-type virus particles have been detected by electron microscopy. The presence of the C-type particles in the placenta of Sprague-Dawley rats is particularly significant because a considerable number of these animals spontaneously develop a variety of malignant tumors in addition to occasional spontaneous leukemias and malignant lymphomas. However, none of these spontaneous tumors reveals the presence of virus particles on electron microscopic examination. The nature of virus particles detected in the rat placenta remains to be determined. It is hypothesized that they may represent the passage of latent, presumably oncogenic, viruses that are transmitted vertically from parents to offspring. In the course of this passage, some particles may be formed, temporarily emerging from their latency before losing their identity, and again being incorporated into the cell genetic components.

3832 AN ANTIGENICALLY RELATED TRYPTIC POLYPEPTIDE FROM SEVERAL MAMMALIAN TYPE C RNA VIRUS p30s. (Eng.) Davis, J. (Flow Lab., Inc., P.O. Box 2226, 1710 Chapman Ave., Rockville, Md. 20852); Gilden, R. V.; Oroszlan, S. *Intervirology* 5(1/2):21-30; 1975.

Antigenic polypeptides were studied to identify the immunogenic regions of the p30 sequence. Type C p30 homologs from rat (RaLV), hamster (HaLV), mouse (MuLV), and gibbon (GaLV) type C viruses were purified by isoelectric focusing. The MuLV isoelectric focused polypeptide (IEFP) was also purified from trypsinized MuLV p30 by isoelectric focusing. The antisera used were from goats im-

munized with purified p30s or Tween-ether-disrupted viruses, rats immunized with Moloney murine sarcoma virus (M-MSV) tumor homogenates, and rats immunized with IEFP. In some experiments, sera were separated into IgG- and IgM-containing fractions or treated with 2-mercaptoethanol. Limited tryptic digestion of p30 antigen (the major internal viral protein) of type C viruses isolated from hamster, rat, and gibbon ape yielded a polypeptide fragment with a molecular weight of approximately 10,000 daltons. Some antigenic determinants with interspecies specificity were retained on these polypeptides, which in serological tests cross-reacted with antibody produced previously against a similar fragment obtained from mouse p30. Exhaustive trypsinization resulted in further fragmentation with concomitant loss of serologic activity. The results suggest that all mammalian type C virus p30s have an antigenically related polypeptide core that is not readily digested by trypsin.

3833 VARIATIONS IN HYBRIDIZATION OF RNA FROM DIFFERENT MOUSE TISSUES AND EMBRYOS TO ENDOGENOUS C-TYPE VIRUS DNA TRANSCRIPTS. (Eng.) Mukherjee, B. B. (Dept. Biology, McGill Univ., Montreal, Canada); Mobry, P. M. *J. Gen. Virol.* 38(1):129-135; 1975.

Various adult tissues (liver, kidney, spleen, uterus, and small intestine) of uninfected BALB/c mice as well as tissue from embryos and newborn animals were examined for RNA complementary to [^{3}H]DNA transcripts, synthesized from an endogenous C-type virus of BALB/c 3T3 mice. The endogenous reverse transcriptase reaction was used to synthesize [^{3}H]DNA copy of the virus genome, and the hybridization was measured by the use of a single strand-specific nuclease (S-1) purified from *Aspergillus oryzae*. Virus-specific RNA was detected in all adult and embryonic tissues tested. However, the RNA extracted from tissues having higher proliferative activity (i.e., spleen, small intestine, uterus and embryonic tissue) hybridized the [^{3}H]DNA probe to a greater extent (18%, 11%, 8%, and 6%-8.5%, respectively) than RNA from tissues with low proliferative activity, such as kidney (5%) and liver (5%). RNA from 14-, 16-, and 18-day embryos hybridized more of the input [^{3}H]DNA probe than RNA from newborn animals. These results support the view that the repression of the virus genome in normal cells is not complete. The results also suggest a correlation between a qualitative or quantitative change in endogenous C-type virus genome transcription pattern and cell proliferation.

3834 INFECTIVE TRANSMISSION AND CHARACTERISATION OF A C-TYPE VIRUS RELEASED BY CULTURED HUMAN MYELOID LEUKAEMIA CELLS. *(Eng.)* Teich, N. M. (Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England); Weiss, R. A.; Mahuddin, S. Z.; Gallagher, R. E.; Gillespie, D.; Gallo, R. C. *Nature* 256(5518):551-555, 1975.

C-type virus particles isolated from long term cultures of myeloid cells (HL23V-1 from peripheral blood smears and HL23V-5 from bone marrow smears) from a patient with acute myelogenous leukemia were characterized and compared with the C-type simian sarcoma-associated virus (SSAV). In addition, the infectious nature of these particles was examined. The establishment of chronically infected virus producing cells required three months and was then only established in four cell lines (human rhabdomyosarcoma cells, fibroblasts from a human embryo, canine thymus cells, and normal rat kidney cells) after inoculation into a wide variety of animal and human cell lines. A more rapid transmission of the virus to two cell lines (a secondary virus) was obtained within three weeks of exposure of these cells to β-propiolactone-inactivated sendai virus. Secondary HL23V-1 infected a wider variety of cells than the primary virus. XC syncytial plaque assay demonstrated the greatest susceptibility to this virus infection in man and rhesus monkey cells; however, a linear dose-response curve was obtained for all cell lines tested. This assay plus radioimmunoassay demonstrated the frequent occurrence of antibodies to HL23V-1 in the human population. In a virus interference test, fetal human lung fibroblasts were infected with HL23V-1 or gibbon ape leukemia virus (GALV) and challenged with murine sarcoma virus pseudotypes, MSV-(HL23V-1) and MSV-(SSAV). Both leukemic viruses reduced the plating efficiency of the two pseudotypes to less than 1% that of uninfected lung fibroblasts indicating the similarity of receptor sites for HL23V-1, SSAV, and GALV. HL23V-1 and HL23V-5 showed early identical patterns in the assays for inhibition of reverse transcriptase activity; they were most strongly inhibited by antiserum prepared against SSV enzyme and less strongly inhibited by anti-GALV enzume. Nucleic acid hybridization experiments demonstrated a relation between viral RNAs and cellular DNA of SSV-infected Kirsten-transformed normal rat kidney cells; t_m values indicated that the hybrids were well-matched in base pairing. The results demonstrate that although HL23V-1 and GALV, and particularly, SSV, are members of the same family, they are not identical.

3835 PARTIAL CHARACTERIZATION OF C-TYPE PARTICLES IN A CELL LINE (WR-9) DERIVED FROM A RAT EPIDERMOID CARCINOMA OF SPONTANEOUS ORIGIN. (Eng.) Sottong, P. (Electro-Nucleonics Lab., Inc. Bethesda, Md. 20014); Woo, J.; Sarma, P. S.; Vaituzis, Z. *Cancer Res.* 35(10):2864-2871; 1975.

A C-type virus that is continuously released from the WR-9 cell line, and was derived from a spontaneous epidermoid carcinoma was purified by means of large-scale tissue culture techniques and high-volume zonal centrifuges. Using relatively pure virus concentrates, partial characterization of the virus was accomplished. Up to 60 l of spent culture medium from relatively low virus-yielding cultures were processed at a time through the Model K ultracentrifuge in order to obtain quantities of virus sufficient for convenient Tween-ether extraction of major polypeptide (30,000 daltons). This structural protein, having group-specific (*gs*) reactivity, was purified and isolated by isoelectric-focusing techniques. A UV absorption peak (A_{280}) was found to be coincident with a major peak of radioactivity at pH 8.6, the isoelectric point (pI) for rat virus *gs*

antigen previously reported by other indicators. Because species-specific (*gs*-1) and cross-reactive (*gs*-3) determinants coexist on this protein, fractions containing the group-specific antigen were identified on the basis of the mammalian interspecies determinant (*gs*-3), using antiserum prepared against Tween-ether-disrupted feline leukemia virus. At the same time, reactivity to the *gs*-1 determinants in identical fractions was observed in complement fixation and gel diffusion assays, using guinea pig antiserum known to contain principally antibodies to rat *gs*-1 determinants. The WR-9 rat virus line may be of use in providing an additional source of C-type particles that are capable of yielding good *gs* reagents.

3836 COMPARISON OF RNA-DIRECTED DNA POLYMERASES FROM XENOTROPIC AND ECOTROPIC VIRUSES. (Eng.) Strickland, J. E. (National Cancer Inst., Frederick Cancer Res. Center, Frederick, Md. 21701); Fowler, A. K.; Hellman, A. *Biochem. Biophys. Res. Commun.* 65(3):1123-1129; 1975.

RNA-directed DNA polymerases from several xenotropic and ecotropic type-C murine viruses were compared. On glycerol sedimentation velocity gradients polymerases from Rauscher murine leukemia virus, AT-124 virus, New Zealand Black virus, and BALB: virus 2 appeared at identical positions as single peaks, indicating similar molecular weights. Immunological comparisons using antisera against DNA polymerases from Rauscher virus and New Zealand Black virus failed to demonstrate significant differences among the viral enzymes tested.

3837 SMOOTH MUSCLE ANTIBODY IN PATIENTS WITH WARTS. (Eng.) McMillan, S. A. (The Laboratories, Belfast City Hosp., Belfast BT9 7AD, Northern Ireland); Haire, M. *Clin. Exp. Immunol.* 21(2):339-344; 1975.

Sera from 54 patients with active common and plantar warts were tested for the presence of commonly found autoantibodies (smooth muscle antibody, antinuclear antibody, antireticulin antibody, and gastric parietal cell antibody). Smooth muscle antibody (SMA) was detected at a significantly higher level (25.9%) than in a control group of an equal number of healthy blood donors matched for age and sex (7.4%), and was in the IgM class. The SMA-positive sera gave a microfilamentous staining pattern, also in the IgM class, on fixed HEp_2 tissue culture cells. Absorption of positive sera with smooth muscle removed both SMA staining and the anti-cellular staining. The finding of SMA and anticellular antibodies of IgM class implies that they are a response to a persistent antigenic stimulus.

3838 METHOD FOR DETERMINATION OF NUCLEOTIDE SEQUENCE HOMOLOGY BETWEEN VIRAL GENOMES BY DNA REASSOCIATION KINETICS. (Eng.) Fujinaga, K. (Sapporo Med. Coll., Japan); Sekikawa, K.; Yamazaki, H. *J. Virol.* 15(3):466-470; 1975.

3839 ON THE FIDELITY OF DNA REPLICATION: CHARACTERIZATION OF POLYNUCLEOTIDES WITH ERRORS IN BASE-PAIRING SYNTHESIZED BY AVIAN MYELOBLASTOSIS VIRUS DEOXYRIBONUCLEIC ACID POLYMERASE. (Eng.) Battula, N. (Fox Chase Cancer Center, Philadelphia, Pa. 19111); Loeb, L. A. *J. Biol. Chem.* 250(12):4405-4409; 1975.

3840 ANALYSIS OF UV-INACTIVATION OF POULTRY SARCOMA VIRUS [abstract]. (Jpn.) Owada, M. (Inst. Microorganism, Osaka Univ., Osaka, Japan); Toyoshima, K. *Virus (Tokyo)* 24(3):281-282; 1975.

3841 PRODUCTION OF TYPE-C VIRUS BY CULTURED HUMAN ACUTE MYELOGENOUS LEUKEMIA (AML) CELLS [abstract]. (Eng.) Gallagher, R. (Natl. Canc Inst., Bethesda, Md.); Salahuddin, Z.; Hall, W.; McCredie, K.; Gallo, R. *Proc. Am. Assoc. Cancer Res* 16:145; 1975.

3842 INFECTIVE TRANSMISSION AND CHARACTERISATIO OF A C-TYPE VIRUS RELEASED BY CULTURED HUMAN MYELOID LEUKAEMIA CELLS. (Eng.) Teich, N. M. (Imp. Cancer Res. Fund, London, England); Weiss, R. A.; Salahuddin, S. Z.; Gallagher, R. E.; Gillespie, D. H.; Gallo, R. C. *Nature* 256(5518):551-555; 1975.

3843 DIFFERENTIAL ACTIVATION BY CELL FUSION OF EPSTEIN-BARR VIRAL AND TYPE-C VIRAL GENOME IN NON-PRODUCTIVE HUMAN LYMPHOID CELLS. (Eng.) Yamamoto, K. (Hokkaido Univ. Sch. Medicine, Sapporo N 15 W 7, Japan); Matsuo, T.; Osato, T.* *Arch. Virol.* 48(2):187-190; 1975.

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3849 EXPRESSION OF FRIEND POLYCYTHEMIA VIRUS-INDUCED ERYTHROID DIFFERENTIATION *IN VITRO* [abstract]. (Eng.) Hankins, W. D. (Vanderbilt Univ. Sch. Med., Nashville, Tenn.); Rosenblatt, P. A.; Krantz, S. B. *Fed. Proc.* 34(3):834; 1975.

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3858 DETECTION OF VIRAL ANTIGENS IN FELINE LEUKEMIAS BY IMMUNE FLUORESCENCE TEST. (Por.) Terrinha, A. M. (Cadeira de Bacteriologia e Virologia, Instituto de Higiene e Medicina Tropical, Lisbon, Portugal); Vigario, J. D.; Moura Nunes, J. F.; Noronha, F. *Arq. Patol.* 46(2/3):299-307; 1974.

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3863 CHARACTERIZATION OF A- AND B-TYPE PARTICLES PRODUCED BY MURINE MYELOMA CELLS [abstract] (Eng.) Robertson, D. (Div. Biol. Biomed. Sci., Washington Univ., St. Louis, Mo.); Dobbertin, D.; Baenziger, N.; Thach, R. E. *Fed. Proc.* 34(3):527; 1975.

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Centre de tri-38041 Grenoble Cedex, France); Mouriquand, J. *Eur. J. Cancer* 11(6):397-402; 1975.

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3879 VIROGENICITY OF K3b STRAIN OF ROUS SARCOMA VIRUS CONVERTED AKR MOUSE CELL [abstract]. (Jpn.) Kowata, J. (Sch. Microbiology, Chiba Univ., Chiba, Japan); Miki, T.; Okazaki, T. *Virus (Tokyo)* 26(3):282; 1975.

3880 PROTEIN KINASE AND ITS REGULATORY EFFECT ON REVERSE TRANSCRIPTASE ACTIVITY OF ROUS SARCOMA VIRUS [abstract]. (Eng.) Lee, S. G. (Northwestern Univ. Med. Sch., Chicago, Ill.); Jungmann, R. A.; Hung, P. P. *Proc. Am. Assoc. Cancer Res.* 16:116; 1975.

3881 SPECIES AND TISSUE SPECIFICITY OF AN INHIBITORY ANTIBODY PREPARED AGAINST PURIFIED PLASMINOGEN ACTIVATOR FROM SV-40 TRANSFORMED HAMSTER CELLS [abstract]. (Eng.) Christman, J. K. (Mt. Sinai Sch. Med., New York, N.Y.); Silverstein, S. C.; Acs, G. *Fed. Proc.* 34(3):532; 1975.

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(Eng.) Flugel, R. M. (Institut fur Virusforschung Deutsches Krebsforschungszentrum, 69 Heidelberg, Im Neuenheimer Feld 280, West Germany); Fischer, H. *J. Natl. Cancer Inst.* 55(4):899-901; 1975.

3883 INDUCTION OF GLIOMAS IN MARMOSETS BY SIMIAN SARCOMA VIRUS, TYPE 1 (SSV-1) [abstract].
(Eng.) Johnson, L., Jr. (Rush-Presbyt.-St. Luke's Med. Cent., Chicago, Ill.); Wolfe, L. G.; Whisler, W. W.; Norton, T.; Thakkar, B.; Deinhardt, F. *Proc. Am. Assoc. Cancer Res.* 16:119; 1975.

3884 GROWTH OF SV 40, ADENO 7 AND SV 40-ADENO 7 VIRUSES IN MONKEY AND HUMAN CELLS AT 29 AND 37 C.
(Eng.) Kutinova, L. (Inst. Sera Vaccines, Prague, Czechoslovakia). *Arch. Virol.* 47(3):257-268; 1975.

See also:

* (Rev): 3614, 3615, 3616, 3646, 3647, 3648, 3649, 3653, 3672
* (Immun): 3894, 3895, 3896, 3897, 3898, 3904, 3905, 3913, 3916, 3922, 3949, 3975, 3980
* (Path): 4012, 4028, 4038, 4079, 4088, 4111
* (Epid-Biom): 4144

3885 AUTOLOGOUS STIMULATION OF HUMAN LYMPHOCYTE SUBPOPULATIONS. (Eng.) Opelz, G. (Sch. Medicine, Univ. California, Los Angeles, Calif. 90024); Kiuchi, M.; Takasugi, M.; Terasaki, P. I. *J. Exp. Med.* 142(5):1327-1333; 1975.

Background stimulation of autologous lymphocytes was studied *in vitro* in a mixed lymphocyte culture (MLC) test. Peripheral blood cells were obtained from healthy blood donors, 20-30 yr of age. T and B cell lymphocyte suspensions were fractionated into B-rich and T-rich subpopulations by the sheep RBC rosetting technique and the goat-antihuman immunoglobulin column fractionation. Unfractionated lymphocytes responded strongly to autologous B-rich cells (stimulation ratio of 15.35, and 3,401 cpm as measured by liquid scintillation spectrophotometry of [^{3}H]thymidine uptake); the response was half of that to allogeneic cells (30.31 ratio, and 6,718 cpm). The B-rich cell background was high (1,536 cpm) while that of T-rich cells was extremely low (98 cpm). The B-rich fraction stimulated the T-rich subpopulation extremely well (ratio, 29.06); autologous unfractionated cells showed less effect (ratio, 7.64). B-rich cells were also more effective than T-rich cells in stimulating allogeneic unfractionated lymphocytes. Similar findings were observed in 11 separate experiments. In an additional eight experiments, T-cell-rich populations, obtained by goat-antihuman immunoglobulin column fractionation, gave a background cpm of 123 $\pm$ 23; unfractionated cells gave 1,158 $\pm$ 187 cpm. Autologous stimulation of T-rich responders by unfractionated stimulators was observed in each instance (mean stimulation ratio, 12 $\pm$ 5). Thus, the results of autologous MLC tests with cells fractionated by both methods were comparable. The results indicate that the background [^{3}H]thymidine uptake in MLC tests can be altered by changing the proportion of T and B cells in the autologous lymphocyte preparation. Reduction of B cells results in a background lowering and an increase of B cells results in a heightening of the background. The authors conclude that stimulation of T cells; probably by autologous B cells, provides the most probable explanation for the alteration of background stimulation.

3886 ANTILEUKOTACTIC PROPERTIES OF TUMOR CELLS. (Eng.) Brozna, J. P. (Univ. Connecticut Health Center, Farmington, Conn. 06032); Ward, P. A. *J. Clin. Invest.* 56(3):616-623; 1975.

To explain why cellular inflammatory responses are defective in the face of malignant tumors and why malignant tumors fail to excite cellular inflammatory responses, a study was made of leukotactic inactivation due to a tumor cell product. Culture medium of *Escherichia coli* was used as the source of chemotactic factor (CF) against which tumor cell fractions were tested for chemotactic factor inactivator (CFI). The tumor cell fractions were obtained by subjecting extracts of sonically disrupted Walker carcinosarcoma and Novikoff hepatoma cells to fractional centrifugation in a discontinuous sucrose gradient. Inactivation experiments were carried out by mixing CF and tumor cell fraction, incubating 30 min at 37 C, and assaying the final mixture for residual chemotactic activity. CFI was found in extracts of both tumors. The CFI directly inactivated the bacterial CF as well as the leukotactic activity associated with C3 and C5 complement fragments and with culture fluids of lectin-stimulated lymphoid cells. The inactivation of the bacterial CF was temperature- and pH-dependent. The CFI was largely associated with the microsomal and cytosol fractions of the tumor cells. CFI activity was also found in neutrophils, alveolar macrophages, and extracts of liver, spleen, and kidney of normal rats. Although CFI was found to be present in ascitic fluids of animals bearing tumors, it was relatively absent in acute inflammatory exudates. The finding of the tumor-associated CFI may explain, in part at least, the tendency of malignant tumor cells to suppress cellular inflammatory reactions.

3887 RESTORATION OF IN VITRO IMMUNE RESPONSIVENESS OF MASTOCYTOMA-SUPPRESSED SPLENOCYTES BY ACTIVATED T CELLS. (Eng.) Kamo, I. (Albert Einstein Medical Center, Philadelphia, Pa. 19141); Patel, C.; Patel, N.; Friedman, H. *J. Immunol.* 115 (2):382-386; 1975.

Because mastocytoma cells are frequently used as an indicator for cell-mediated immune responses, and since the mastocytoma-induced immunosuppression appears to be mediated by a soluble factor(s), the mechanisms involved were investigated in detail. Spleen cells from normal DBA/2 mice pretreated with a soluble factor from mastocytoma cells or from ascitic fluid of mastocytoma-bearing mice were markedly impaired in terms of antibody formation to SRBC *in vitro*. Such immunosuppression by mastocytoma homogenates or ascitic fluid was reversed when syngeneic T cells activated to SRBC were added to the cultures, but not when peritoneal exudate cells or anti-θ-treated normal splenocytes were used. Activated T cells, as well as normal B lymphocytes prepared from spleens of lethally irradiated mice reconstituted with bone marrow cells, were less sensitive to the immunosuppressive factor than nonactivated T cells. The ability of educated T cells to restore immunocompetence of suppressed spleen cells *in vitro* suggests that the target of the immunosuppressive factor from mastocytoma cells may be nonactivated T cells, especially those involved in T cell helper function.

3888 IMMUNOLOGIC INDUCTION OF MALIGNANT LYMPHOMA: IDENTIFICATION OF DONOR AND HOST TUMORS IN THE GRAFT-VERSUS-HOST MODEL. (Eng.) Gleichmann, E. (Abteilung fur Experimentelle Pathologie, Medizinische Hochschule Hannover, 3 Hannover, Karl-Wiechert-Allee 9, West Germany); Gleichmann, H.; Schwartz, R. S.; Weinblatt, A.; Armstrong, M. Y. K. *J. Natl. Cancer Inst.* 54(1):107-116; 1975.

Primary lymphoid tumors were induced by inoculation of parental line spleen cells into H-2-incompatible F_1 hybrid mice. The F_1 recipients received ip injections of approximately 50 x 10^6 parental spleen cells weekly for four weeks. The genotypes of lym-

phomas arising in 19 different parent--F_1 combinations were determined with cytotoxic antisera against H-2 specificities of donor and host. Additional chromosome marker studies established the reliability of tumor genotyping by the cytotoxicity test. According to H-2 typing, 12 primary lymphomas were of donor type, 66 of host type, and 14 of intermediate type. As a group, those parent--F_1 combinations in which donor-type lymphomas developed (group 1) showed a higher degree of histocompatibility between donor and host than those combinations in which donor-type lymphomas failed to appear (group 2). Allogeneic inhibition may have suppressed the development of donor-type tumors in the combinations of group 2. The development of malignant lymphomas of donor-type in the graft-*vs*-host reaction supports the concept of lymphomagenesis as a consequence of persistent stimulation by antigen.

3889 LEUKAEMOGENESIS AND REGENERATION OF LYMPHOID SYSTEM IN (C3H x AKR/T1ALD)F1 HYBRIDS RESTORED WITH PARENTAL BONE MARROW AND THYMIC CELLS. (Fre.) Legrand, E. (Unite INSERM 117, Fondation Bergonie, 33076 Bordeaux, France); Kressmann, M. C.; Duplan, J. F. *Int. J. Cancer* 15(4):572-587; 1975.

To determine the roles played by bone marrow and thymic cells in the repopulation of lymphoid organs and in the development of leukemia, a study was carried out using sub-lethally irradiated (C3H x AKR/TIALD)F_1 mice whose lymphoid system was restored with parental bone marrow (BM) cells with or without thymic cells. Identification of host or donor origin of leukemic cells in this sytem was made possible through the occurrence of a metacentric marker in the TIALD substrain. Leukemias in the hybrids appeared either as lymphosarcomas (LST) in the thymus or as extra-thymic leukemias (LET). After X-irradiation with four weekly doses of 175 R each, the incidence of LST increased from the original level of 2% to a final level of 94%. The incidence of total leukemia (LST + LET), 7% in unirradiated animals and 94% in irradiated animals, became 55, 56, and 100% when the irradiated hybrids were restored with 8 x 10^6 to 10^7 BM cells of syngeneic, C3H, or AKR origin, resp. In the animals given AKR BM cells, 75% of the lymphosarcomas originated from the donor cells. The inhibitory efficiency of the three different sources of BM cells appeared to be related to their respective tendencies toward spontaneous malignant transformation. When 2 x 10^7 AKR or C3H thymic cells were injected together with BM cells, the leukemogenesis was altered. This effect was indirect, since these cells were not actually involved in the malignant transformation. The percentage of LST was significantly reduced and the mean survival improved in hybrids restored with C3H thymic cells mixed with AKR or C3H BM cells. The AKR thymic cells were less efficient. In both cases, however, the incidence of LET increased at the expense of the LST. Thymic cells did not change the kinetics of repopulation in thymus and lymph-node by the BM cells, except when C3H thymic cells were mixed with T1ALD BM cells; in this case, the lymph-node repopulation was temporarily enhanced. Different hypotheses were offered to explain the effect of thymic cells on leukemogenesis, namely, enhanced recovery of the post-irradiation immunological deficiency, transfer of virus by the AKR thymic cells, and influence of thymic cells on the maturation and/or differentiation of the lymphoid cells.

3890 NONSPECIFIC RESISTANCE TO TUMOR ALLOGRAFT. (Eng.) Rejthar, A. (Faculty Medicine, J. E. Purkyne Univ., 656 91 Brno, Czechoslovakia); Wotke, J.; Rejtharova, A.; Jaskova, J. *Neoplasma* 22(3):273-278; 1975.

The effects of an increased volume of reticulohistiocyte system and macrophage activation in the recipient after treatment with BCG and Zymosan on the course of antitumor concomitant allograft-immunity reaction were studied. The results were verified on C57B1/6J mice with immunosuppression due to whole body irradiation (^{60}Co, 500 rads). A substantially lower host resistance against the tumor allograft was shown by prophylactic administration of BCG and Zymosan. Transplantation of macrophages syngeneic to the host failed to affect the latter's resistance to subsequent tumor allograft. The irradiated host's reactivity was regenerated with a suspension of spleen cells or purified small lymphocytes, but transplantation of syngeneic macrophages remained without effect. The difference observed in the host's reactivity followed the increase in lymphocyte volume and that following BCG and Zymosan activation of the macrophage system indicates a relatively small role for the macrophage system in tumor allograft resistance in contrast to the essential role played by specific immunity mechanisms mediated in the transplantation reaction mainly by lymphocytes.

3891 DEFECTS IN CELL-MEDIATED IMMUNITY DURING GROWTH OF A SYNGENEIC SIMIAN VIRUS-INDUCED TUMOR. (Eng.) Howell, S. B. (Natl. Cancer Inst., Bethesda, Md. 20014); Dean, J. H.; Law, L. W. *Int. J. Cancer* 15(1):152-169; 1975.

Four assays of tumor-specific cell-mediated immunity in BALB/c mice were compared during growth of a syngeneic simian-virus-40-induced tumor, mKSA. Major differences were found in immunity detected by the tumor neutralization test (the Winn test), direct tumor challenge, the microcytotoxicity assay, and the ^{51}chromium-release lymphocytotoxicity assay. Progressive growth of the neoplasm followed by loss of immunity (the eclipse phenomenon) was documented with the Winn test. It was established that this eclipse pehnomenon represented a lesion in the T-cell system of tumor-bearing hosts. This lesion was found to be specific and unrelated to anatomic tumor location. The ability to produce graft-*vs*-host reactions and the ability to respond to mitogens were generally intact in tumor-bearing animals. Cells capable of recognizing mKSA tumor antigens and reconstituting an immune response following surgical removal of tumor or upon transfer to normal mice were found in the spleens of mice bearing advanced tumors. No suppressor cells that might account for the eclipse phenomenon could be demonstrated. Tumor-bearer serum did not block neutralizing activity of immune spleen cells in

the Winn test, and immune cells were capable of neutralizing tumor even in tumor-bearing hosts. The possibility that the lesion is intrinsic to T-cell precursors of effector cells is suggested by the ability of T-cells from immune mice to generate neutralizing activity in tumor-bearing hosts.

3892 IMMUNE SURVEILLANCE DIRECTED AGAINST DEREPRESSED CELLULAR AND VIRAL ALLOANTIGENS. (Eng.) Martin, W. J. (Natl. Cancer Inst., Bethesda, Md.). *Cell. Immunol.* 15(1):1-10; 1975.

A commentary on genetically-determined tumor susceptibility is presented and attempts are made to explain such susceptibility in terms of impaired immune surveillance due to a failure of normal repression of genetic loci coding for cell surface components. Certain cell surface antigens are found on tumor cells that are not found on normal cells of most strains of mice. Some of the cell surface antigens are believed to be products of endogenous C-type viruses. Successful repression of these viral or cellular cell surface antigens by normal cells, and derepression of the alloantigen on malignant cells could provide anti-tumor immunity. It has been shown that endogenous C-type virus expression correlates with increased susceptibility to tumors. An explanation for this observation is presented which is based on immune surveillance against derepressed viral alloantigens on a restricted basis.

3893 IMMUNODEPRESSION AND MALIGNANCY. (Eng.) Stutman, O. (Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021). *Proc. Int. Cancer Congr. 11th.* Vol. 1 *(Cell Biology and Tumor Immunology).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Coscinelli, N. New York, American Elsevier, 1975, pp. 275-279.

Evidence supporting the view that malignant development, and not tumor growth or spread, is controlled by an immune mechanism is reviewed. Athymic nude (nu/nu) mice were used to test the effects of immune deficiencies on tumor development and on tumor induction by several oncogenic and viral agents. In a pilot study, the spontaneous tumor incidence of 35 male and 30 female nude mice in a CBA/H background was 26 and 13%, respectively. When the viable yellow gene that favors spontaneous tumor development was inserted into the nude background, no significant difference in lung adenoma incidence was observed between nude and control mice. The incidence of spontaneous malignancies in nude mice was comparable to that in immunologically normal controls. Experiments with chemical carcinogens demonstrated no significant differences in tumor incidence (except for thymic lymphomas) between immunologically incompetent nude mice exposed to 3-methylcholanthrene or urethan and normal heterozygotes (n/+). In another series of experiments (ongenic virus-induced tumors), no significant differences were observed between nu/nu and nu/+ mice (both of C57BL/6 background) when the animals were tested for susceptibility to leukemia by Friend virus; both strains remained resistant to leukemia development. When nude mice in BALB/c or CBA/H background were infected with the Moloney strain of murine sarcoma virus, all mice developed tumors; however, nu/+ mice induced regression of the growing tumor within 10-12 days after tumor appearance, demonstrating that tumor regression is a thymus-dependent event. In addition, a significant difference in tumor development occurred in nude mice infected with polyoma virus and nu/+-CBA/H controls. Thus, the results with chemical and viral carcinogens support those obtained with immunodepression procedures; no significant differences in tumor incidence or latent periods for tumor development are observed between immunologically deficient mice and their normal nu/+ siblings. The authors conclude that the role of "immune surveillance" in tumor development is not fully substantiated by clinical and experimental data.

3894 DISSEMINATED HERPES SIMPLEX IN UNTREATED MULTIPLE MYELOMA. PARADOX OF PRESENT CONCEPTS OF IMMUNE DEFECTS. (Eng.) Deresinski, S. C. (Santa Clara Valley Medical Center, 751 S. Bascom Ave., San Jose, Calif. 95128); Stevens, D. A. *Oncology* 30(4):318-323; 1974.

The case of a 64-yr-old man with disseminated herpes simplex virus infection documented by direct immunofluorescence, and untreated multiple myeloma with abnormal immunoglobulins is presented. Skin tests performed on the 13th hospital day with purified protein derivative of *Mycobacterium tuberculosis* (5 TU), coccidioidin (1:100), histoplasmin, and candida antigens were nonreactive. Reports of infections with intracellular pathogens in myeloma patients are rare; pyogenic infections have been amply documented. The untreated disease has been considered a relatively pure defect in humoral immunity. Review of present knowledge suggests that cell-mediated immunity is of paramount importance in treating this virus infection. Immune defects in multiple myeloma, and its infectious complications, may be more complex than suggested by current concepts of this disease.

3895 LEUKEMIA VIRUS-INDUCED IMMUNOSUPPRESSION: SCANNING ELECTRON MICROSCOPY OF INFECTED SPLEEN CELLS. (Eng.) Farber, P. (Albert Einstein Medical Center, Philadelphia, Pa.); Specter, S.; Friedman, H. *Science* 190(4213):469-471; 1975.

Spleen cells, as well as other lymphoid tissue of Friend leukemia virus (FLV)-infected mice were scanned by electron microscopy (EM) to determine the lymphocyte populations that might be related to the infectious process and to the development of immunosuppression. Balb/c mice were infected by iv injection of FLV. At various times thereafter, representative mice were killed, and their spleen lymphocytes were processed by Ficoll-Hypaque centrifugation and prepared for EM scanning. In a parallel series of experiments, representative animals from each group were immunized with

SRBC, and the number of antibody plaque-forming cells (PFC) in the spleens of these animals was determined by the localized hemolytic assay in agar gel. The spleen cell suspension was also examined by fluorescent microscopy for cells bearing surface immunoglobulin receptors, theta antigen, and FLV-induced tumor-associated antigen. Alteration of cell type was evident within a few days after FLV infection. Nearly all splenocytes were abnormal in appearance by 17-30 days after infection, with most showing a spongy topography. These changes paralleled the marked decrease in immunosuppression quantitated by PFC: 9.8×10^3 PFC in noninfected mice; 0.8×10^3 and less than 0.1×10^3 PFC 17 and 30 days postinfection, respectively. The appearance of virus-associated surface antigen on individual splenocytes and the decrease of splenocytes with surface immunoglobulin also paralleled the morphological changes. There was a consistent decrease in the cells staining with anti-theta serum during the infection. The results are consistent with earlier findings concerning histologic and ultrastructural features of lymphoid tissue from FLV-infected mice.

3896 CORRECTION OF A MURINE MAMMARY TUMOR VIRUS-ASSOCIATED IMMUNOLOGICAL DEPRESSION BY SELECTIVE IMMUNOSUPPRESSION WITH CYTOSINE ARABINOSIDE. (Eng.) Griswold, D. E. (Smith Kline & French Lab., 1500 Spring Garden St., Philadelphia, Pa. 19101); Kopp, J. S.; Manning, J. S.; Heppner, G. H. *Cancer Res.* 35(10):2670-2673; 1975.

The association of mammary tumor virus (MTV) infection and cell mediated immunity (CMI) was investigated by the use of a drug regimen designed to inhibit humoral immunity but not CMI. In addition, CMI function was independently assessed by contact sensitization to oxazolone and by phytohemagglutinin (PHA)-induced lymphocytic blastogenesis. Two MTV negative mouse strains (C3HeB/FeJ and BALB/c) and two MTV-positive (C3H/HeJ and BALB/cfC3H) strains were studied. Hypersensitivity to methylated bovine serum albumin (MBSA) was induced in mice by two 1 mg doses of MBSA at an interval of one week. The challenge dose of 200 µg was administered into the footpad 14 days after the first MBSA injection. While MTV-negative animals responded well to MBSA and MTV-positive animals responded poorly, both strains responded well to oxazolone; however, the MTV-positive mice demonstrated a greater response. When spleen cells from female MTV-positive and -negative mice were tested to PHA by their ability to incorporate tritiated thymidine, the response was greater among those cells from both strains of MTV-infected mice than those from their MTV-free costrains. Again, MTV-positive animals responded better to PHA than the MTV-negative (24.9 cpm for BALB/cfC3H and 10.4 cpm for C3H/HeJ *vs* 5.9 cpm for BALB/c and 1.9 cpm for C3HeB/FeJ). The participation of the humoral blocking factor in the MBSA response was investigated by a low dose regimen of cytosine arabinoside (ara-C). Doses of 10, 20, and 40 mg/kg ara-C had no effect on the MTV-negative mice, whereas 10 mg stimulated MBSA hypersensitivity in the MTV-positive mice. These results suggest a normal CMI response compromised by a strong humoral blocking component in the C3H/HeJ (MTV-positive) mice and that the observed diminished response to MBSA in MTV-infected animals is not due to direct depressing of the CMI reactivity. MTV infection may facilitate the production of interfering or blocking humoral immunity.

3897 IMMUNIZATION AGAINST MAREK'S DISEASE USING MAREK'S DISEASE VIRUS-SPECIFIC ANTIGENS FREE FROM INFECTIOUS VIRUS. (Eng.) Lesnik, F. (Veterinary Univ., Komenskeho 71 Kosice, Czechoslovakia); Ross, L. J. N. *Int. J. Cancer* 16(1): 153-163; 1975.

Immunity against Marek's disease was conferred by the use of noninfectious materials extracted with nonionic detergents from cells infected with the attenuated strain of Marek's disease virus (MDV). Antibody-free Rhode Island Red chicks were inoculated im at one wk of age with 0.1 ml cell extracts emulsified in Freund's complete adjuvant and were given a second inoculation one wk later without adjuvant. Protection against natural infection was obtained in groups inoculated with both soluble (not sedimented at 100,000 x g/2 hr) and insoluble antigens present in Nonidet P40 (NP40) extract, but only with the insoluble fraction of deoxycholate extract. The results suggest that the immunizing antigens can be partially solubilized with 0.5% NP40 and that the growth and spread of MDV are reduced in immunized chickens.

3898 REGRESSION OF WARTS: AN IMMUNOLOGICAL STUDY. (Eng.) Pyrhonen, S. (Dep. Virol., Univ. Helsinki, Finland); Johansson, E. *Lancet* 1 (7907):592-596; 1975.

The duration and regression of warts in relation to the occurrence of wart-virus antibodies were studied in 173 patients with warts who were observed for 3-6 mo. In 80% of the patients, wart-virus antibodies were present and could be measured by immunodiffusion; in 20% these could also be detected by complement-fixation (CF) techniques. The mean duration of the warts in patients with CF antibodies was 0·6 yr and in the others 1·9 yr. The occurrence of CF antibodies (IgG) was associated with rapid healing; 75% of these patients were cured during the first two months of the observation period. In contrast, of the patients with antibodies measurable only by the immunodiffusion technique (IgM and/or low titers of IgG), only 16% were cured during the first two months, and they had a fairly constant cure-rate (approximately 9%/mo) during six months of observation. The results indicate that the cure of warts is partly connected with immunological phenomena, especially with the presence of CF antibodies. In other cases wart regression may be mainly a nonimmune process, perhaps due to a limited lifespan of wart cells.

3899 PROLIFERATIVE CHARACTERISTICS OF MONOBLASTS GROWN *IN VITRO*. (Eng.) Goud, T. J. L. M. (Univ. Hosp., Leiden, The Netherlands); van Furth, R. *J. Exp. Med.* 142(5):1200-1217; 1975.

A previous study in which mononuclear phagocyte colonies were grown in a liquid culture system was continued; the present study concerned the proliferative behavior of the monoblast and promonocyte in colonies. The cell-cycle times of both cell types were determined on the basis of four independent methods. The resulting values all showed excellent agreement: for the monoblast 11.0-11.9 hr and for the promonocyte 11.4-12.8 hr. The DNA synthesis time found for the two cell types amounted to 5.7 hr for the monoblast and 5.5 hr for the promonocyte. The duration of the other phases of the cell cycle of the proliferating mononuclear phagocytes proved to be: G2 phase, 0.6 hr; mitosis phase, 1.8 hr; and G1 phase, 3.5-3.8 hr. The individual colonies showed a biphasic pattern of colony growth, an initial phase of rapid proliferation followed by a stage with markedly decreased growth rate. In the initial stage only monoblasts were present in the colony; when the growth rate decreased, promonocytes and macrophages appeared. These observations support an earlier conclusion that the monoblast is without doubt the precursor of the promonocyte. Colony size varied widely. The main factor underlying this variation proved to be the lag time between the start of the culture and the time point at which the colony-forming cells began to divide. Mathematical analysis showed that the variation in colony size probably did not arise from heterogeneity of the population of colony-forming cells. A mathematical approach was used to determine the proportion of self-replicating and differentiating cells among the dividing monoblasts and promonocytes in the colony. The results indicated that initially *in vitro* the majority of the cells of both types were self-replicating cells, but later an increasing proportion of the dividing cells gave rise to another, more mature type of cell. On the basis of the conclusion that the monoblast initiates the mononuclear phagocyte colony, the number of monoblasts (2.5×10^5) present *in vivo* was estimated to be half the number of the mononocytes. In view of this ratio, the most likely pattern for the proliferation of mononuclear phagocytes in the bone marrow is that a monoblast divides once, giving rise to two promonocytes which in their turn divide once and form two nonproliferating monocytes.

3900 THE ORIGIN AND ROLE OF BLOOD-BORNE MONOCYTES IN RATS WITH A TRANSPLANTED MYELOGENOUS LEUKAEMIA. (Eng.) Gauci, C. L. (Chester Beatty Res. Inst., Clifton Ave., Belmont, Sutton, Surrey, SM2 5PX U.K.); Wrathmell, A.; Alexander*, P. *Cancer Lett.* 1(1):33-37; 1975.

The origin and role of blood-borne monocytes associated with the growth of transplantable myelogenous leukemia (SAL) in August rats were investigated. Nonadherent leukemic blast cells of leukocyte enriched buffy coat preparations from heparinized blood of rats with SAL were separated from the macrophage-like blast cells which adhered to the culture vessel. Approximately 2.5% of the cells recovered from 10^5 cell/mm^3 of white cell populations of leukemic rats were macrophages. Leukemia did not result in normal rats from the injection of 2×10^5 of these detached macrophages. SAL (2×10^5) was injected iv into a group of 18 rats at varying intervals; three rats from each group were then killed and their blood analyzed. In these rats, the number of blood monocytes rose progressively (20 times that of normal rats a day before their death) as the disease progressed. When the buffy coat of August x Marshall F_1 hybrids bearing SAL leukemia was cultured and the adherent and nonadherent cells treated with August anti-Marshall serum, only the macrophages bound to the allo-antisera. Binding of the immunoglobulin to the surface of living cells was determined by immunofluorescence. A similar experiment was performed with August rats that had been irradiated with a total body dose of 900 R x-rays and in whom the bone marrow had been reconstituted by the iv injection of 5×10^7 August x Marshall F_1 bone marrow cells. Seven days later, 10^5 SAL cells were injected into the rats; ten days later the blood was found to contain more than 10^5 leukemic blast cells/mm^3. The buffy coat gave rise from 5 to 6% macrophages and all the cells were found to be of the F_1 phenotype using the anti-Marshall serum assay. These experiements prove that monocytes present in the leukemic blood are of host origin and not derived from the SAL leukemic cells. In addition, the inflammatory reaction and the delayed hypersensitivity response to the ip injection of oyster glycogen of rats bearing SAL leukemia showed no difference from that of normal rats, demonstrating that blood monocytes of rats with SAL function normally in inflammatory situations. The authors conclude that the host response which is responsible for the monocytosis differs from that associated with the entry of monocytes into immunogenic sarcomas.

3901 RELEASE AND SPECIFICITY OF INHIBITORS FOR MACROMOLECULAR SYNTHESES FROM VARIOUS SUSPENSION TUMOR STRAINS. (Eng.) Werner, D. (German Cancer Research Center, Heidelberg, West Germany); Schulte, M. *Eur. J. Cancer* 11(7):521-522; 1975.

Evidence for the release of a peptide that inhibits DNA and protein synthesis, from cells of various tumor strains is presented. Freshly-harvested cells, at the end of a first 90 min incubation, showed no incorporation of ^{3}H-thymidine and ^{14}C-amino acids. Ehrlich ascites tumor cells (in Go, G+, or Karzel) Walker 256 ascites cells, L-929 murine fibrocytes, and Zajdela rat hepatoma cells were studied. The cells immediately recovered their high rates of DNA and protein syntheses when the "conditioned" medium was renewed at the beginning of the second 90 min incubation. During the second 90 min incubation period, a second cessation of the macromolecular syntheses was seen in all the cell strains studied. The cells did not recover the high rates of syntheses when incubated in the medium "conditioned" by another cell strain, indicating that the inhibitors released are not cell-specific. The unspecific nature of the released factors is not consistent with the previously suggested involvement in autoregulation. The factors described here could cooperate with unknown cell specific factors to produce autoregulation *in vivo*.

3902 ATTEMPTS TO COMPARE THE EFFECTIVENESS OF BLOCKING FACTORS AND ENHANCING ANTIBODIES *IN VIVO* AND *IN VITRO*. (Eng.) Hasek, M. (Inst. of Experimental Biology and Genetics, Czechoslovak Acad. of Sciences, 160 00 Prague 6, Czechoslovakia); Chutna, J.; Sladecek, M.; Machackova, M.; Bubenik, J.; Matousek, V. *Transplantation* 20(2):95-100; 1975.

To determine whether a blocking serum factor may play a role in the induction of immunological tolerance, newborn AVN strain rats were injected with 2 x 10^8 bone marrow cells from Lewis strain rats, tolerance was assayed by transplantation of Lewis skin grafts, and sera collected from tolerant animals were tested for ability to block *in vitro* cytotoxic effects of immune lymphocytes. The immune lymphocytes used in these tests were obtained from AVN rats which had been sensitized with Lewis skin graft, and the target cells used were Rous sarcoma virus-induced rat RSL sarcoma cells. Of 39 sera from tolerant rats, only 24 showed blocking activity, indicating that neonatal tolerance induction did not depend upon the presence of blocking factors in the serum. To determine next whether blocking factor may be responsible for immunological enhancement of tumor grafts, eight blocking and 14 nonblocking sera were each injected in two 1-ml amounts (1 ml iv, 1 ml ip) 2-4 hr before im inoculation of 5 x 10^7 RSL tumor cells, and tumor sizes were determined 13 days later. The effects of immune serum obtained from AVN rats immunized repeatedly with Lewis lymph nodes served for comparison. It was found that the growth of allogeneic tumors was markedly enhanced after the passive transfer of tolerant or immune sera and that there was no difference between results obtained with blocking and nonblocking sera from tolerant rats. The results suggested that there is no relationship between blocking factors measured *in vitro* and enhancing activity measured *in vivo*.

3903 AUTOANTIBODIES IN PATIENTS WITH BRONCHIAL CARCINOMA. (Eng.) Hodson, M. E. (Cardiothoracic Inst., Fulham Road, Brompton, London SW3 6HP, England); Turner-Warwick*, M. *Thorax* 30(4):367-370; 1975.

Smooth muscle antibody production was studied in 105 patients with bronchial carcinoma of different histological types in order to relate the antibody prevalence to a number of clinical features. Squamous tumors were found in 50 patients, oat cell tumors in 25, adenocarcinomas in 19, and undifferentiated tumors in 11 patients. Sera from patients were diluted 1/10 and examined for antinuclear, smooth muscle, and reticulin antibodies by indirect double layer immunofluorescence. The prevalence of antinuclear antibodies (12%), smooth muscle antibodies (12%), and reticulin antibodies (4%) in the sera of carcinoma patients did not differ significantly from the controls. Sera from patients with undifferentiated tumors had significantly increased titers of smooth muscle antibodies (27%) when compared to controls (5%). Elevated antinuclear levels were observed in adenocarcinoma patients (31% versus 5% for the controls). No correlation was found between autoantibody titers and the various clinical features (including age, sex, smoking habits, duration and nature of symptoms, presence of hemoptysis, neuropathy, finger clubbing, weight loss, lymph node enlargement, and liver involvement).

3904 ANTIBODY TO HERPES-LIKE VIRUS IN SARCOIDOSIS. (Eng.) Mitchell, D. N. (Brompton Hosp., Fulham Road, London SW3 6HP, England); McSwiggan, D. A.; Mikhail, J. R.; Heimer, G. V. *Am. Rev. Respir.* 111(6):880-882; 1975.

Anti-herpes-like virus (HLV) antibody titers in serum samples from 70 consecutive patients with sarcoidosis were measured and compared with titers found in 70 age-, sex-, and race-matched controls. Samples were drawn at the time of diagnosis, and antibody titers were determined by indirect immunofluorescence. Antibody was detected in all 70 sarcoid and control sera. Of the 70 sarcoid patients, 49 (70%) had anti-HLV antibody titers < 1:600; 21 (30%) had titers ≥ 1:600. Of the 70 matched controls, 62 (89%) had titers < 1:600, and only eight (11%) had titers ≥ 1:600. Although 30 sarcoid patients (43%) had titers higher than the matched control, the difference in the geometric mean titer of the patient and control groups was only 0.5 of a two-fold dilution. The difference in the geometric mean titer between patient and control subject did not vary significantly with sex, race, or type of sarcoidosis. However, differences between sarcoid and control sera were greater among nonwhite patients, who often had a more florid sarcoidosis. Among the 45 sarcoid patients tested for anti-HLV antibody titers after an interval of 18-60 mos, 39 (74%) had unchanged titers; four had a higher titer (by one dilution); and three had a lower titer (by one dilution). There was no evidence of changes in titer associated with progression, regression, or attainment of inactivity of the sarcoidosis. It is concluded that raised anti-HLV antibody titers in patients with sarcoidosis are most likely to be related to the ability of these patients to show enhanced humoral antibody responses.

3905 THE ROLE OF INTERFERON IN THE SPONTANEOUS REGRESSION OF FRIEND VIRUS INDUCED LEUKEMIA. (Eng.) Furmanski, P. (Michigan Cancer Foundation, 110 East Warren Ave., Detroit, Mich. 48201); Juni, S.; Hall, L.; Rich, M. A. *Proc. Soc. Exp. Biol. Med.* 150(1):11-13; 1975.

The effect of Statolon and polyinosinic-polycytidilic acid (Poly-IC), and the role of interferon in spontaneous regression of Friend virus-induced murine leukemia was investigated. Random-bred male Swiss/ICRHa weanling mice inoculated with conventional Friend murine leukemia virus (MuLV) develop splenic leukemia, which only very rarely regresses spontaneously. A stable variant of Friend MuLV induces leukemia that spontaneously regresses in a large proportion of the infected animals. Conventional or variant Friend MuLV-infected mice were treated with either 4 mg Statolon or with 25 μg Poly-IC inoculated iv three days postinfection. In mice infected with conventional Friend MuLV and treated with Statolon or Poly-IC, the regression rate of leukemia was 10

and 23%, respectively. The rate of spontaneous regression was 38% of the variant strain-induced leukemia, but neither Statolon nor Poly-IC treatment (47 and 34%, respectively) had any significant effect on the spontaneous regression. No significant effect of Statolon or Poly-IC on the incidence of leukemia in conventional or variant Friend MuLV-infected mice was observed. Assays of interferon activity in sera from regressed mice was observed. Assays of interferon activity in sera from regressed mice were made using both the plaque reduction and yield reduction tests. No significant amounts of interferon were detected in the regressed sera above that observed in the control sera. The conventional or variant Friend MuLV did not induce interferon activity above the level in the control sera 6, 30, and 50 hr postvirus inoculation. Sera from variant Friend MuLV-induced leukemic mice at 28-35 days postvirus inoculation, the time just prior to spontaneous regression, did not contain any significant interferon activity. The authors conclude that interferon does not play a significant role in the spontaneous regression of Friend virus leukemia.

3906 SYNTHESIS OF α-FETOPROTEIN BY RAT ASCITES HEPATOMA CELLS. (Eng.) Kanai, K. (First Dept. Medicine, Faculty of Medicine, Univ. Tokyo, Tokyo, Japan); Endo, Y.; Oda, T.; Kaneko, Y. *Ann. NY Acad. Sci.* 259:29-36; 1975.

Two aspects of α-fetoprotein (AFP) synthesis in rat hepatomas were examined. In experiment 1, the intracellular site of AFP synthesis in hepatoma cells was studied using a cell-free protein synthesizing system; in experiment 2, the effect of cyclic nucleotides on AFP production in cultured cells was studied. Rat ascites hepatoma cells were derived from the AH-66 strain transplanted ip to male Donryu rats. In experiment 1, [^{14}C]leucine was incorporated into the AFP fraction when hepatoma ribosomes were used in the system; ribosomes prepared from normal liver incorporated little radioactivity into AFP. The incorporation of [^{14}C]leucine into the AFP fraction by membrane-bound polysomes was 20-90 times higher than by free polysomes. In experiment 2, 0.5mM of dibutyryl-3',5'-adenosine monophosphate (DBcAMP) inhibited the growth of tumor cells; this inhibitory effect was enhanced by theophylline. The incorporation of [^{14}C]leucine into the proteins of tumor cells increased by 60% in the presence of DBcAMP. DBcAMP also increased the production of AFP by hepatoma cells. These experiments confirm the synthesis of AFP by tumor cells. Labeled AFP in the incubation medium indicated that AFP was synthesized mainly by the membrane-bound ribosomes of tumor cells and secreted into the medium, suggesting that AFP may have some function in the circulating blood.

3907 α-FETOPROTEIN IN YOLK SAC TUMOR. (Eng.) Tsuchida, Y. (Dept. Pathology, Faculty of Medicine, Univ. Tokyo, Tokyo, Japan); Endo, Y.; Urano, Y.; Ishida, M. *Ann. N.Y. Acad. Sci.* 259: 221-233; 1975.

The phenomenon of α-fetoprotein (AFP) synthesis in benign and malignant teratomas was studied. Only those serum AFP levels over 200 ng/ml were considered positive. A survey of AFP occurrence in 88 cases revealed that 33 were malignant; the tumor appeared in the mediastinum in one case, in the retroperitoneum in one, in the sacrococcygeal region in 14, in the testicle in 11, and in the ovary in six. Of the malignant teratomas, 25 were AFP-positive and eight were AFP-negative. Of the 55 benign cases, nine were AFP-positive and 46 were AFP-negative. AFP-positive benign tumors were seen only at the age of one month or younger. There were no AFP-positive cases in patients older than two months of age. Thus, the determination of AFP concentrations appears valuable in the differential diagnosis between benign and malignant teratomas, unless the patient is at the age of one month or younger. Of 19 cases of AFP-positive teratocarcinomas for which histological studies were carried out, 16 showed a typical yolk sac tumor (endodermal sinus tumor). It is proposed that the occurrence of AFP in teratocarcinomas is best explained by the concept of yolk sac tumor, because it is known that large amounts of AFP are synthesized not only by the fetal liver but also by the yolk sac during early embryonic life, and because the diagnosis of yolk sac tumor implies that the tumor is of yolk sac origin morphologically. More direct evidence of AFP synthesis was demonstrated by immunofluorescent techniques in one of the cases. A bright immunofluorescence was seen only in that cell layer that has long been defined as of yolk sac origin.

3908 THE ASSOCIATION OF CARCINOEMBRYONIC ANTIGEN AND PERIPHERAL LYMPHOCYTES. (Eng.) Papatestas, A. E. (Mount Sinai Hosp., 100th St., and Fifth Ave., New York, N.Y. 10029); Kim, U.; Genkins, G.; Kornfeld, P.; Horowitz, S. H.; Aufses, A. H., Jr. *Surgery* 78(3):343-348; 1975.

The potential value of combined carcinoembryonic antigen (CEA) assays and lymphocyte counts in cancer detection was investigated. A significant association between (CEA) titers and peripheral lymphocyte counts was observed in 148 simultaneous determinations. The association was present in a high cancer risk study group of 97 patients with myasthenia gravis and in a control group of 51 patients with granulomatous disease of the bowel, ulcerative colitis, and colonic neoplasms. A highly significant difference in the percentage of positive CEA assays in relation to lymphocyte counts was noted both in the study and control groups. In the study group CEA was positive in seven of 41 patients (17%) with counts above 2000 mm^3, and in 26 of 56 (43%) of those with lower counts (X^2=9.06, $p < 0.005$). The corresponding percentages in the control group were 20 and 61% ($X^2 = 5.60$, $p < 0.025$). A significant difference between the means of lymphocytes in groups with different CEA titers also was found ($F = 6.77$, $p < 0.05$). The finding of lower peripheral lymphocytes and/or higher titers of CEA in groups with increased risk of cancer, i.e., severe myasthenia gravis, patients with thymomas and patients with long history of granulomatous disease of the bowel, suggests an association between the results of the two tests and

cancer risk. The observations indicate that the yield of CEA assay in cancer detection may be higher in patients with low lymphocytes, and that these determinations used in conjunction may serve better as diagnostic and prognostic aids in patients with known neoplasms or in high cancer risk groups.

3909 A CARCINOFETAL ANTIGEN LOCATED ON THE MEMBRANE OF CELLS FROM RAT INTESTINAL CARCINOMA IN CULTURE. (Eng.) Martin, F. (Lab. Experimental Medicine, Faculty of Medicine, Boulevard Jeanne d'Arc, 21000 Dijon, France); Knobel, S.; Martin, M.; Bordes, M. *Cancer Res.* 35(2):333-336; 1975.

Heteroantisera were produced in rabbits by ip immunization with cultivated cells from five lines of rat intestinal carcinomas. The tumors included colonic carcinomas induced in BD-IX rats by 1,2-dimethylhydrazine and duodenal carcinomas induced in BN and Lewis rats by *N*-methyl-*N*-nitro-*N*-nitrosoguanidine. The sera was made specific by *in vivo* absorption in syngeneic rats. On immunofluorescence, these sera recognized a membrane-associated antigen common to five different intestinal carcinomas and to fetal intestine. The antigen was not detected in noncancerous adult intestine, nonintestinal fetal tissues, or three nonintestinal tumor cell lines. The cancer and tissue specificity of the antisera used in this study were not demonstrated in heteroantisera prepared by more conventional methods.

3910 RELATIONSHIP BETWEEN CARCINOEMBRYONIC ANTIGEN AND BLOOD GROUP ANTIGENS A, B, AND LEWIS. (Eng.) Mach, J.-P. (Institut de Biochimie, Universite de Lausanne, Lausanne, Switzerland); Singh, K.; Perrinjaquet, J.; Carrel, S.; Merenda, C.; MacDonald, D.; Holburn, A. *Ann. N.Y. Acad. Sci.* 259:389-403; 1975.

Evidence is presented that different blood group antigenic sites are bound to carcinoembryonic antigen (CEA) molecules of some CEA preparations. The methods used were double diffusion, immunoelectrophoresis, radioimmunology, Sepharose 6B gel filtration, and isoelectric focusing. It was found by double diffusion that a monospecific anti-CEA antiserum that did not react with blood group A glycoprotein formed a precipitin line of identity between five CEA preparations containing different blood group antigens A, B, or Lewis. When a human IgG fraction from an anti-blood group A antiserum was tested against the same antigens, precipitin lines were obtained only with blood group A glycoprotein and with one of the CEA preparations, CEA III, which was known to contain blood group A antigenic sites. Similarly, in immunoelectrophoresis, CEA III reacted with both anti-CEA and anti-blood group A antisera, whereas A-glycoprotein reacted only with anti-blood group A. In radioimmunological studies, involving binding of ^{125}I-labeled CEA V (which also contained blood group A sites) with anti-blood group A antiserum, absorption of the antiserum with blood group A cells, but not with B or O cells, abolished the reactivity of the antiserum with the CEA. The possibility that anti-CEA antibodies contaminating the anti-blood group A serum could have been responsible for the binding with CEA V was excluded by the finding that three different CEA preparations failed to inhibit the binding. When ^{125}I-labeled CEA 101, containing blood group B activity, was eluted from a Sepharose 6B column and the different fractions were tested for radioactivity and for ability to bind anti-CEA and anti-blood group B antisera, it was found that the peak of radioactivity was identical with that observed for nine other CEA preparations fractionated on this column. If the blood group specificity were due to aggregation with contaminating blood glycoproteins, the CEA molecules associated with these aggregated glycoproteins should have been eluted earlier from the column; this was not observed. Fractions of CEA separated by isoelectric focusing showed, despite great charge heterogeneity of the preparations, that the percentage binding by both anti-CEA and anti-blood group antisera remained the same in all fractions. Blood group A antigenic determinants of CEA III preparation were sensitive to periodate oxidation, while CEA-antigenic determinants were almost unaltered by this oxidative procedure. Further experiments revealed no evidence for the presence in test sera of complexes between CEA preparations and corresponding anti-blood group antibody. The findings were all consistent in indicating that different blood group antigenic sites are linked to CEA molecules. At the same time, not all CEA preparations appeared to carry blood group sites. It was not clear whether the antigenic determinants reacting with specific anti-blood group antisera are authentic blood group heterosaccharide side chains or are "blood group-like" antigens.

3911 ONCOFETAL PROTEIN ACCOMPANYING IRRADIATION-INDUCED SMALL-BOWEL ADENOCARCINOMA IN THE RAT. (Eng.) Stevens, R. H. (Radiation Res. Lab., 14 Medical Lab., Univ. Iowa, Iowa City, Iowa 52242); England, C. W.; Osborne, J. W.; Cheng, H. F.; Richerson, H. B. *J. Natl. Cancer Inst.* 55(4):1011-1013; 1975.

A tumor-associated protein was found in tissue derived from an X-irradiation-induced adenocarcinoma in the small bowel of male Holtzman rats. The protein was associated with the cell membranes of the tumor tissue. It shared common antigenic determinants both with a protein similarly prepared from 17-19 day rat embryos, and with a perchloric acid-soluble protein isolated from the serum of these tumor-bearing rats.

3912 LOCATION BY IMMUNOELECTRON MICROSCOPY OF CARCINOEMBRYONIC ANTIGEN ON CULTURED ADENOCARCINOMA CELLS. (Eng.) Herberman, R. B. (Natl. Cancer Inst., Bethesda, Md. 20014); Aoki, T.; Cannon, G.; Liu, M.; Sturm, M. *J. Natl. Cancer Inst.* 55(4): 797-799; 1975.

The tissue-culture cell line HT-29, derived from a primary colon adenocarcinoma and previously shown

to secrete carcinoembryonic antigen (CEA), was examined by immunoelectron microscopy for the location of CEA in relation to the cells. CEA was closely adjacent to the plasma membrane within 10 nm, a location indistinguishable from that of alloantigens and other tumor-associated antigens. Previous reports that CEA was rarely demonstrated on the cell surface may have resulted from interference with labeling by the heavy coating on the cells used previously.

3913 A MIXED-IMMUNOGLOBULIN ROSETTE TECHNIQUE FOR THE DETECTION OF ANTIBODY TO FELINE ONCORNAVIRUS-ASSOCIATED CELL MEMBRANE ANTIGEN. (Eng.) Mackey, L. (Leukemia Res. Unit, Univ. Glasgow, Scotland); Jarrett, W.; Wilson, L. *Cancer Res.* 35(4):1064-1068; 1975.

A novel technique for detecting immunoglobulin attached to cell membrane antigens is presented. Cultured feline leukemia virus (FeLV)-infected lymphoid cells are incubated with the test serum, exposed to a rabbit anti-cat IgG serum, and the antigen-antibody reaction is detected by mixing the lymphoid cells with SRBC that have been sensitized with cat anti-SRBC serum. The presence of cat immunoglobulin on the lymphoid cells is registered by the formation of SRBC rosettes. The experiments involved feline lymphoid cells from the FL74 cell line chronically infected with FeLV of subgroups A, B, and C, and dog lymphoid cells from the CT45S line infected with FeLV5. An experiment to detect antibodies to feline oncornavirus-associated cell membrane antigens (FOCMA) by the mixed immunoglobulin rosette (MIR) method indicated a sigmoidal relationship between serum dilution and rosette formation. A comparison of the indirect immunofluorescence and MIR tests showed a close correlation, with the MIR method exhibiting a higher sensitivity. Sera from 22 uninfected kittens were examined at a 1:4 dilution; when the mean percentage of rosettes was $\pm$ 2.7 at this dilution. This indicates that 25% rosette formation lies above the nonspecific range. When sera from 32 cats with naturally occurring lymphoid cancers were examined, an additional seven containing positive antibody were detected with the MIR test. There was also good correlation of the indirect immunofluorescence titer and the MIR titer when FeLV-infected dog cells were employed. The results showed that MIR is approximately ten times more sensitive than indirect immunofluorescence for the detection of antibody to FOCMA. Its advantages include the accurate quantitation of rosettes and the lack of expensive equipment of labeled sera; the major disadvantage is the greater length of time required for the 2-stage process.

3914 HETEROPHILE ANTIGENS AND ANTIBODIES IN TRANSPLANTATION AND TUMORS. (Eng.) Milgrom, F. (Dept. Microbiology, State Univ. New York, Buffalo, N.Y.); Kano, K.; Fjelde, A.; Bloom, M. L. *Transplant. Proc.* 7(2):201-207; 1975.

Paul-Bunnell antigen, identified by the agglutination of Forssman-negative bovine RBC by infectious-mononucleosis sera, was examined for its occurrence in other cells. Using gel double diffusion, it was shown that reactions of mononucleosis sera with bovine stroma extract produced two partially superimposed lines. One of these was related to sheep or horse stroma extracts. Thus, bovine RBC contained two Paul-Bunnell antigens; sheep and horse RBC contained only one. Using a procedure of cytolysis of target cells in agar gel, the mononucleosis serum revealed Paul-Bunnell antigen in murine T cells and also in θ-bearing EL-4 and L#2 murine lymphoma cells. Based on absorptive capacity, the lymphoma cells contained more antigen than the normal T cells. In the ox, the Paul-Bunnell antigen appeared on all or most cells, including RBC, liver and kidney cells, lymphoid cells, and platelets. In man, the antigen was absent in all cells under normal physiologic conditions. It appeared that human lymphoid cells acquired the antigen as a result of transformation during the course of infectious mononucleosis. It also appeared that it might be because of the Paul-Bunnell antigen and antibodies that infectious mononucleosis is a benign disease. Further studies revealed the presence of Paul-Bunnell antigen in spleens of 26/59 lymphoma-leukemia patients. However, these lytic antibodies proved to be directed toward Forssman antigen rather than Paul-Bunnell antigen. No satisfactory explanation was available, although it was suggested that the lack of formation of Paul-Bunnell antibodies in patients whose cells contain the antigen may account for the malignancy of these diseases compared to infectious mononucleosis. Another type of heterophile reaction was shown by sera of allograft recipients. Thus, sera of human volunteers injected with allogenic leucocytes and then subjected to skin allografts showed increased agglutinin titers for sheep, guinea-pig, and rat RBC. In 10/22 renal allograft recipients, titers of hemagglutinins to rat RBC increased eight-fold after transplantation. Heterophile antibodies of a human or rabbit allograft recipient were found to be absorbed by the donor's tissues as well as by unrelated allogeneic tissues, but not by the recipient's own tissues. Thus, these antibodies can be viewed as transplantation antibodies. The role of heterophile antibodies in homograft rejection appears possible and seems to warrant further exploration.

3915 THYMUS LEUKAEMIA ANTIGEN CONTAINS β2-MICROGLOBULIN. (Eng.) Ostberg, L. (Dept. Med. Physiol. Chem. Immunol., Univ. Uppsala, Sweden); Rask, L.; Wigzell, H.; Peterson, P. A. *Nature* 253-(5494):735-737; 1975.

In investigating the possibility of gene duplications in the mouse major histocompatibility complex, thymus leukemia (TL) antigens were isolated and characterized. An antiserum against TL antigens 1 and 3 (TLa-1,3) was raised by injection of BALB/c mice with A/Sn thymus cells. The resulting antiserum was absorbed with A/Sn spleen and liver cells until its titer tested in a ^{51}Cr-release cytotoxicity assay was completely abolished; the elimination of all non-TL antibodies was confirmed using a sensitive protein A assay. Highly specific antibodies against β2-microglobulin were obtained by passage of a rabbit anti-β2-microglobulin antiserum over a Sepharose-coupled human β_2-microglobulin column. The immune

complex formed with the TLa-1,3 antiserum and thymus cell antigens contained two types of molecules of molecular weights 50,000 and 12,000, respectively. The large TL antigen polypeptide chain was of a size similar to the H-2 alloantigen-carrying polypeptide chain. In addition, the immune complex induced by TLa-1,3 antiserum contained a small polypeptide chain of a size similar to β_2-microglobulin. Experiments to investigate this relationship involved the isolation and adsorption of TL antigens. The immunosorbent-purified thymus cell surface antigens contained a small amount of aggregated material and antigens of three distinct molecular weights: 50,000, 37,000, and 12,000. The immune complexes were formed with the TLa-1,3 antiserum and contained only the 50,000 and 12,000 dalton components. Subjection of the TLa-1,3 ^{125}I-labeled immune complexes and ^{131}I-labeled β_2-microglobulin to polyacrylamide gel electrophoresis illustrated indistinguishable electrophoretic mobility and apparent homogeneity, as did two-dimensional electrophoresis. The results demonstrate that H-2 and TL-antigens share β_2-microglobulin as a common subunit, with a similar size large polypeptide chain carrying the distinctive antigenic determinants.

3916 TUMOR-SPECIFIC TRANSPLANTATION ANTIGEN(S) OF BOVINE ADENOVIRUSES. (Eng.) Panigrahy, B. (Baylor Coll. Med., Houston, Tex.); McCormick, K. J.; Trentin, J. J. *J. Natl. Cancer Inst.* 54(2):449-451; 1975.

Protection against Bovine Adenovirus type 3 tumor formation (both induced primary and transplantable tumor cells) was studied. Syrian hamsters (LSH/Lak) were immunized with bovine adenovirus types 1, 2, 3 and (BAV-1,-2,-3); human adenovirus type 12 (A-12); simian adenovirus type 7 (SA7); and chicken-embryo-lethal-orphan (CELO) virus. In the primary tumor prevention experiments, newborn hamsters were given 2.3 x 10^5 plaque-forming units (pfu) of BAV-3sc. They were then injected three times with either BAV-1 (1.3 x 10^5), BAV-2 (1.5 x 10^6), BAV-3 (2.3 x 10^6), A-12 (3.2 x 10^7), SA7 (3.2 x 10^7), CELO (3.9 x 10^8), or with control Madin-Darby bovine kidney cell (MDBK) extracts. (Viral titers were expressed as either pfu or 50% tissue culture infective dose.) No animal inoculated and immunized with BAV-3 developed tumors; immunization with BAV-1 and -2 allowed 44% and 50%, respectively, of the animals to develop tumors as compared with control MDBK extract-immunized animals, whose tumor incidence was 90%. Immunization with A-12, SA7, or CELO did not inhibit primary tumor formation. In the transplantation immunity tests, weanling hamsters were immunized with either BAV-1, -2, -3, or control MDBK cells. When these animals were challenged with 10^3 to 10^7 cells from BAV-3 tumor, tumor formation was observed. The animals immunized with BAV-3 gave a 50% tumor-producing dose of cells 2-3 logs above control, while BAV-1 or -2 immunization gave a 50% tumor-producing dose of cells of about 2 logs above control. These studies indicate that BAV-1, -2, -3 induce cross-reactive transplantation antigens that do not cross-react with those induced by oncogenic adenoviruses of either avian, simian, or human origin.

3917 T CELLS IN CHRONIC LYMPHOCYTIC LEUKAEMIA. (Eng.) Nowell, P. C. (Univ. Pennsylvania Sch. Med., Philadelphia); Daniele, R.; Winger, L.; Rowlands, D. T., Jr.; Gardner, F. *Lancet* (7912):915; 1975.

The occurrence of T cells in a 38-yr-old woman with chronic lymphocytic leukemia (CLL) was investigated. Except for an episode of hemolytic anemia in 1969, requiring steroid therapy for six weeks, the disease was quiescent for 12 years. Thereafter, a series of viral and bacterial infections occurred, and ultimately resulted in her death one year later. Studies of peripheral lymphocytes, including phytohemagglutinin (PHA) responsiveness, E rosette formation, EAC rosette formation, and surface immunoglobulins were performed on four occasions during the last two years of life. Three studies exhibited a predominance of B-cells (i.e., a pattern consistent with typical cell). The other study was performed during an episode of acute pseudomonas sinusitis. She was receiving antibiotics and prednisone which had been gradually reduced from 45 mg/day to 30 mg/day during the preceding two weeks. The study showed few B cells (EAC rosettes 8%) and predominance of T cells (E rosettes 79%), with 4-5 times the normal number in the circulation. These cells did not respond to PHA. The acute infection may have been responsible for the increase in the number of T cells and their failure to respond to PHA. It is also postulated that the steroid therapy was responsible for the unresponsiveness to PHA. The temporary presence of neoplastic T cells in the blood, capable of forming E rosettes but unresponsive to PHA, cannot be ruled out. Further investigation on the production of T cells in CLL is indicated.

3918 CHRONIC LYMPHOCYTIC LEUKAEMIA OF T-CELL ORIGIN: IMMUNOLOGICAL AND CLINICAL EVALUATION IN ELEVEN PATIENTS. (Eng.) Brouet, J.-C (Hospital Saint-Louis, 75475 Paris Cedex 10, France); Sasportes, M.; Flandrin, G.; Preud'Homme, J.-L.; Seligmann, M. *Lancet* 2(7941):890-893; 1975.

Eleven patients with chronic lymphocytic leukemia are reported. The identification of the leukemic cells was performed with seven different membrane markers for either T or B lymphocytes. The reactivity of the leukemic T cells with three different heteroantisera to T cells differed from patient to patient but was homogeneous in individual cases. This finding suggests that the leukemic lymphocytes belonged to a single subset of T cells. These lymphocytes responded to allogeneic cells in some of these patients. In contrast, stimulation by nonspecific mitogens (phytohemagglutinin or pokeweed) was poor in most patients. Two patients were affected with the prolymphocytic type of chronic lymphocytic leukemia, but a characteristic clinical and hematological pattern was found in nine patients. The blood and marrow infiltration was moderate and the proliferating T lymphocytes had a high content of lysosomal enzymes in all patients and cytoplasmic granules in six cases. Other unusual features included massive splenomegaly (five patients) skin lesions (four patients), and major neutropenia (four

patients). The results suggest that chronic lymphocytic leukemia of T-cell origin may not be as rare as it has been previously considered.

3919 A SURFACE MEMBRANE DETERMINANT SHARED BY SUBPOPULATIONS OF THYMOCYTES AND B LYMPHOCYTES. (Eng.) Stout, R. D. (Stanford Univ. Sch. Medicine, Stanford, Calif. 94305); Yutoku, M.; Grossberg, A.; Pressman, D.; Herzenberg, L. A. *J. Immunol.* 115(2):508-512; 1975.

Utilizing a quantitative fluorescence assay with the fluorescence-activated cell sorter (FACS), it was demonstrated that a rabbit antiserum obtained by immunization with cells of a mouse IgM-producing plasma cell tumor (MOPC104E) is reactive with at least two surface determinants (designated Th-B and ML2) on subpopulations of normal murine lymphocytes. The ML12 determinant was restricted to B lymphocytes. The Th-B determinant was shared by splenic B lymphocytes and a large subpopulation of thymocytes, the latter of which expressed a 3-fold higher density of Th-B on their surface than did the B lymphocytes. Neither Th-B nor ML2 were found on peripheral T cells or on brain, liver, or kidney cells. The available evidence suggesting that Th-B may be a stem cell determinant that is lost upon maturation is discussed.

3920 POSSIBLE T-CELL ORIGIN OF LYMPHOBLASTS IN ACID-PHOSPHATASE-POSITIVE ACUTE LYMPHATIC LEUKAEMIA. (Eng.) Ritter, J. (Universitatskinderklinik, Martinistrasse 52, D-2 Hamburg, West Germany); Gaedicke, G.; Winkler, K.; Beckmann, H.; Landbeck, G. *Lancet* 2(7924):75; 1975.

Three patients with acid-phosphatase-positive leukemia were tested with immunological cell-surface markers. Blast cells from all patients formed spontaneous rosettes with SRBC and with *Vibrio cholerae* neuraminidase (VCN) SRBC. These results plus the response of these patients to therapy recommended for acute lymphatic leukemia (ALL) indicate that acid-phosphatase-positive leukemia is a subgroup of ALL probably involving thymus-derived lymphocytes. This disease is likely to be identical with Sternberg's sarcoma. We suggest the term acid-phosphatase-positive acute lymphatic leukemia/lymphosarcoma for this type of acute leukemia.

3921 CLASSIFICATION OF MALIGNANT LYMPHOMAS BY MEANS OF MEMBRANE MARKERS. (Eng.) Huber, H. (Medizinische Univ.-Klinik, Anischstrabe 35, A-6020 Innsbruck, Austria); Michlamayr, G.; Huber, C. *Acta Neuropathol.* [*Suppl.*] *(Berlin).* 6:31-36; 1975.

The distribution of B and T lymphocytes was studied in patients with chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphomas, and Hodgkin's disease. B lymphocytes were evaluated autoradiographically with ^{125}I-labeled anti-immunoglobulin (Ig) antisera and ^{125}I-labeled heat-aggregated gamma globulin (AGG). T lymphocytes were assessed by their capacity to form rosettes with unsensitized neuraminidase-treated SRBC. In some studies, the proliferating capacity of lymphocytes from patients with Hodgkin's disease or infectious mononucleosis was evaluated by the combined use of ^{3}H-thymidine labeling and membrane markers. In most CLL patients, the leukemic lymphocytes behaved as B cells; thus, 17 of 18 patients had very high percentages of blood lymphocytes reacting with AGG as well as with anti-Ig sera, while the percentage of T lymphocytes was inversely related to the lymphocyte count. The density of membrane receptors on B lymphocytes was reduced in these patients, and a monoclonal proliferation of neoplastic cells was observed in seven of nine patients studied. A marked increase of blood lymphocytes with membrane-bound Ig and receptors for AGG was noted, however, in only four of 16 patients with non-Hodgkin's lymphoma. In contrast, cell suspensions of affected lymph nodes showed high numbers of lymphocytes reacting with AGG and anti-Ig-antisera in ten of 12 patients. The density of membrane receptors was not reduced in this group although lymphoma cells were monoclonal with respect to their Ig coat. The B/T cell ratio of blood lymphocytes of patients with Hodgkin's disease was comparable to that of normal controls. The percentage of B lymphocytes was slightly higher in affected lymph nodes than in uninvolved lymph nodes. A preferential proliferation of T lymphocytes was seen in patients with Hodgkin's disease and in patients with infectious mononucleosis. A T lymphocyte response to an as yet unknown stimulus, perhaps accompanied by a reduced lymphocyte life span, may play an important role in the pathogenesis of Hodgkin's disease.

3922 INHIBITION OF THE MITOGENIC RESPONSE OF NORMAL PERIPHERAL LYMPHOCYTES BY EXTRACTS OR SUPERNATANT FLUIDS OF A *HERPESVIRUS SAIMIRI* LYMPHOID TUMOR CELL LINE. (Eng.) Neubauer, R. H. (Litton Bionetics, Inc., Kensington, Md. 20795); Wallen, W. C.; Rabin, H. *Infect. Immun.* 12(5): 1021-1028; 1975.

A *Herpesvirus saimiri*-infected marmoset lymphoid cell line (MLC-1) was examined for the presence of soluble factors which might affect lymphocyte functions and, therefore, relate to the pathogenesis of lymphoma *in vivo*. MLC-1 cells, cell extracts, and culture fluids reduced the spontaneous DNA synthesis of normal peripheral blood lymphocytes and completely inhibited their response to phytohemagglutinin (PHA). Suppression of PHA response was demonstrated against a variety of human and nonhuman primate species, with 90-95% inhibition occurring at dilutions of extract as great as 1:5,120. Inhibition of this type was also demonstrated using extracts of 2 of 5 other lymphoblastoid cell lines. Physical-chemical characteristics of the active factor(s) revealed a non-sedimentable, non-dialyzable, trypsin-resistant molecule that was stable at 56 C for 30 min but inactivated at 80 C for 30 min. The factor(s) also exerted an effect on some but not all established lymphoblastoid cell lines, where DNA, RNA, and protein synthesis were all inhibited, with DNA synthesis being the most affected (95% suppression). Cellular respiration was not affected by the presence of the factor(s), and the inhibition of DNA synthesis was reversible after 24 hr. Purified human interferon did not reduce the PHA response of normal owl monkey peripheral blood lymphocytes and was less effective

against an established lymphoblastoid cell line than the MLC-1 extract. Antiviral activity was also demonstrated in the preparations and may represent interferon, which these cells are known to produce at low levels.

3923 CHANGES IN LYMPHOCYTE SURFACE IMMUNOGLOBULINS IN MYELOMA AND THE EFFECT OF AN RNA-CONTAINING PLASMA FACTOR. (Eng.) Chen, Y. (Veterans Administration West Side Hosp., P.O. Box 8195, Chicago, Ill. 60680); Bhoopalam, N.; Yakulis, V.; Heller, P. *Ann. Intern. Med.* 83(5):625-631; 1975.

A study was carried out on the mechanism of conversion of the surface immunoglobulins on circulating lymphocytes of patients with multiple myeloma. The patients consisted of 13 men and one woman; ten had IgG, and four had IgA myeloma. Seven of the globulins were of the kappa type; the other seven were lambda. Normal human IgG, IgA, IgM, and kappa and lambda Bence Jones proteins were purified and used for preparation of rabbit antisera, rendered anti-isotypically specific by immunoabsorption procedures. Antisera to myeloma proteins of five patients were prepared and rendered anti-idiotypically specific by similar procedures. The anti-isotypic sera were used for visualization of surface immunoglobulin by direct immunofluorescence; the anti-idiotypic sera, for showing monoclonal myeloma globulins by indirect immunofluorescence. Peripheral blood lymphocytes were isolated by differential centrifugation on Ficoll-Hypaque gradients. The number of B cells with surface immunoglobulins was expressed as percentage of the total number of lymphocytes per cubic millimeter. RNA-rich extracts were prepared from plasma of myeloma patients by a phenol extraction procedure. Experiments on digestion of RNA-rich preparations were performed with pancreatic RNase, DNase, and pronase. *In vitro* tests for conversion of surface immunoglobulins by the RNA preparations were carried out by incubating 10^6 lymphocytes in 0.1 ml barbital-buffered saline (BBS) with 1 mg RNA in 0.1 ml BBS for 30 min at 37 C. After three washings, surface immunoglobulin of the lymphocytes was determined by indirect immunofluorescence. Concentrations of actinomycin D or cycloheximide that are known to suppress synthesis of RNA and of protein, respectively, were added in some tests. In the 14 patients with myeloma, there was a statistically significant reduction in the percentage of lymphocytes with surface immunoglobulins of the various isotypes to about one-third of that in normal controls. When, however, anti-idiotypic antisera to the respective myeloma globulins were used for visualization of surface immunoglobulins, a large number of surface immunoglobulin-carrying lymphocytes were detected. The possibility of absorption of these monoclonal surface immunoglobulins from the surrounding plasma was excluded by showing their resynthesis after removal from the cells by trypsinization. The change in the character of surface immunoglobulins was reproduced on normal lymphocytes by the RNA-rich extracts; this effect was inhibited by RNase and cycloheximide. These findings suggest the possiblity that an RNA-containing plasma factor transmits information for synthesis of surface immunoglobulins between myeloma cells and normal lymphocytes. This mechanism may contribute to the dysfunction of B lymphocytes in patients with myeloma, leading to immunologic deficiency.

3924 LIGAND-INDUCED REDISTRIBUTION OF LYMPHOCYTE MEMBRANE GANGLIOSIDE GM1. (Eng.) Revesz, T. (ICRF Tumour Immunology Unit, Zoology Dept., University Coll., London WC1E 6BT, UK); Greaves, M. *Nature* 257(5522):103-106; 1975.

The redistribution of monosialo-gangliotetraosylceramide (GM1) into aggregates and caps, using cholera toxin (choleragen) and labeled antibodies as ligands, was studied. All lymphocytes, monocytes and granulocytes studied bound choleragen to their surface and uptake was rapidly saturated at 20 C. Binding was inhibited by purified GM1. The biologically inactive choleragenoid bound almost as effectively as choleragen. Human lymphocytes showed pronounced redistribution into discrete caps over a wide range of concentrations. Mouse lymphocytes showed caps only with the lower concentrations used. By incubating mouse spleen lymphocytes with low concentrations (10^{-4}-10^{-2} μg ml^{-1}) of choleragen at 37 C followed by the two antibody layers at 4 C in the presence of azide it was possible to demonstrate capping on approximately 50% of reactive cells. Creation of more GM1 binding sites for choleragen by neuraminidase pretreatment, into GM1, or by direct insertion of GM1 into cells, inhibited capping of GM1 on human tonsil cells. Capping of immunoglobulin molecules on lymphocytes has been reported to be inhibited by a combination of colchicine and cytochalasin. These drugs had precisely the same effect on GM1 redistribution. After either GM1 insertion or neuraminidase treatment acute leukemia cells showed pronounced capping at 10^3 μg GM1/ml but not at higher concentrations.

3925 HUMAN TUMOR-LYMPHOCYTE INTERACTION *IN VITRO*: BLASTOGENESIS CORRELATED TO DETECTABLE IMMUNOGLOBULIN IN THE BIOPSY. (Eng.) Vanky, F. (Dept. Tumor Biology, Karolinska Inst., Stockholm, Sweden); Trempe, G.; Klein, E.; Stjernsward, J. *Int. J. Cancer* 16(1):113-124; 1975.

Binding of radioiodinated anti-immunoglobulin (Ig) reagent assayed by acid elutable radioactivity was shown in 18 of 44 cell suspensions (41%) prepared from surgical specimens of human tumors. Aliquots of these biopsies were admixed to autologous lymphocytes and in 13 cases they induced stimulation of DNA synthesis. In only one of these 13 cases was the anti-Ig reagent bound, while among the 26 biopsies with low or no binding capacity 12 (46%) were stimulatory, indicating that immunoglobulin-containing biopsies are not stimulatory. Differentiated tumors were among those which had low mounts of Ig or none at all. Malignant tumors such as the myeloma and osteosarcomas contained Ig. Experiments on 32 lymphocyte preparations from different lymphoid organs suggest that the

immunoglobulin detected in the tumor cell suspension is not derived from the infiltrating lymphoid cells. The results support previous studies indicating that the presence of Ig in tumor cells is related to the degree of malignancy.

3926 E AND EAC ROSETTING LYMPHOCYTES IN PATIENTS WITH CARCINOMA OF BRONCHUS. I. SOME PARAMETERS OF THE TEST AND OF ITS PROGNOSTIC SIGNIFICANCE. (Eng.) Anthony, H. M. (Sch. Med., Leeds, England); Kirk, J. A.; Madsen, K. E.; Mason, M. K.; Templeman, G. H. *Clin. Exp. Immunol.* 20(1): 29-40; 1975.

T and C3 receptor B lymphocytes in normal donors and in patients with bronchial carcinoma were estimated. Using peripheral blood lymphocytes separated by a Ficoll method and suspended in saline, means of 77.1%, standard deviation (s.d.)= 5.2, E rosettes (T lymphocytes), and 20.1% (s.d. 6.7) SRBC rosettes (B lymphocytes) were obtained with 11 healthy donors (nine men, two women; 22-59 yr). Poorer SRBC-rosette formation resulted from higher centrifugation speeds during the washing of lymphocytes or RBC, insufficient chilling, or rough handling. The presence of 5% albumin in the final mixture stabilized the rosettes and brought a constant subpopulation of B lymphocytes into rosetting. In 31 patients with bronchial carcinoma who, at the time of diagnosis, had SRBC-rosette percentages below 1 s.d. of the mean for normal donors, the length of survival was significantly shorter than in those with normal or high values. The same was true for those in whom null cells were detected. In each case the correlation effect was mainly found in the group of 17 patients with squamous carcinoma, as opposed to those with oat cell carcinoma (eight patients). The complete enumeration of T and B lymphocytes may contribute to the *in vitro* investigation of immune status in cancer patients.

3927 ACTIVATION OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES BY CONCANAVALIN A DEPENDENCE OF MONOCYTES. (Eng.) Hedfors, E. (Serafimer Hosp., P.O. Box 12700, S-112 83 Stockholm, Sweden); Holm, G.; Pettersson, D. *Clin. Exp. Immunol.* 22(2):223-229; 1975.

The potentiation of *in vitro* concanavalin A (Con A)-induced DNA synthesis in human peripheral lymphocytes by blood monocytes was subjected to further investigation. The lymphocytes were prepared from defibrinated venous blood by sedimentation through gelatine, followed by iron treatment to remove phagocytic cells. Acid-treated glass beads were coated with human IgG followed by rabbit anti-human IgG antiserum and were used for absorption and elution of the desired T cells fraction from the lymphocyte preparation. The monocytes were prepared from heparinized venous blood by sedimentation through gelatin, followed by centrifugation on a bovine serum albumin gradient. Monocytes were separated from the top layer fraction by adherence methods using plastic tissue culture flasks. The monocytes were treated with mitomycin C and were used in combination with autologous lymphocytes at varying ratios and varying total numbers of cells per culture tube. The culture medium consisted of supplemented RPMI 1640 containing 15% human AB serum. DNA synthesis was determined on the basis of ^{14}C-thymidine incorporation. It was found that the activation of the human lymphocytes or of purified lymphocytes by Con A was highly potentiated by the presence of the autologous monocytes. The optimal lymphocyte:monocyte ratio was 1:1 when the incorporation of thymidine was expressed as total incorporation per culture tube and 1:10 when expressed per lymphocyte. A 5- to 10-fold increase of total DNA synthesis was noted in the presence of 10-90% monocytes. The mechanism responsible for the effect was not known but among those offered were reduced survival of lymphocytes in monocyte-depleted cultures, increased stimulating potency of Con A when bound to monocytes, shortening of cell cycle of Con A-activated lymphocytes by the presence of monocytes, or selective removal of T cells participating in primary response to Con A during fractionation of lymphocytes on the Ig-anti-Ig column. The findings may help to explain the wide variations in Con A responsiveness of human peripheral lymphocytes on the basis of contamination with varying amounts of monocytes.

3928 DISTRIBUTION OF CONCANAVALIN A RECEPTOR SITES ON SPECIFIC POPULATIONS OF EMBRYONIC CELLS. (Eng.) Roberson, M. (Dept. Biology, California State Univ., Northridge, Calif. 91324); Neri, A.; Oppenheimer, S. B. *Science* 189(4203):639-640; 1975.

The distribution of concanavalin A (Con A) receptor sites on the micromere and nonmigratory embryonic cell types (macromeres and mesomeres) of the sea urchin embryo were identified by phase contrast fluorescence microscopy. The distribution of Con A receptor sites was random on all three embryonic cell populations. However, 95% of the cells treated with fluorescein isothiocyanate-conjugated Con A before fixation manifested capped or highly clustered receptor sites on the micromeres. The distribution of receptor sites remained random on the mesomeres and macromeres. The results indicate that Con A receptor sites are more mobile on specific populations of malignant-like migratory embryonic cells.

3929 LEUKAEMIA IN CHILDREN AND THEIR GRANDPARENTS: STUDIES OF IMMUNE FUNCTION IN SIX FAMILIES. (Eng.) Till, M. M. (Inst. Child Health, London, England); Jones, L. H.; Pentycross, C. R.; Hardisty, R. M.; Lawler, S. D.; Harvey, B. A. M.; Soothill, J. F. *Br. J. Haematol.* 29(4):575-586; 1975.

Seven of 500 children with acute leukemia seen over a 15-yr period were known to have a close relative with leukemia or lymphoma. In each case the affected relative was a grandparent of the child, 6 of the 7 being paternal grandparents. The following laboratory tests were performed on the sera or blood cells of most of the parents, sibs, and/or children: total and differential WBC count, serum immunoglobu-

lins, lymphocyte response to phytohemagglutinin, bactericidal capacity of polymorphonuclear leukocytes, yeast opsonization test, antistreptolysin titers, isohemagglutinin titers, and HL-A typing. The fathers in these six families, who had two-affected first-degree relatives, had lower lymphocyte counts and higher serum IgA concentrations than paired controls. Atopy, repeated infectious and rheumatic disease were common among the parents and their sibs. The findings suggest a possible immunodeficiency basis for leukemia in these families, and perhaps also for acute lymphoblastic leukemia of childhood in general. In the only family in which three generations, including both leukemic patients, were available for HL-A typing, the affected grandson had not inherited either of his affected grandmother's haplotypes.

3930 CARCINOFETAL HUMAN ISOFERRITINS. (Eng.) Drysdale, J. W. (Tufts Univ. Sch. Medicine, Boston, Mass. 02111); Alpert, E. *Ann. NY Acad. Sci.* 259:427-434; 1975.

The structural basis for possible alterations in the phenotypic expression of isoferritin in cancer cells was investigated. Ferritin was isolated from human tissues and HeLa cells grown in culture and fractionated by isoelectric focusing in sucrose density gradients in polyacrylamide gel; the subunit composition of ferritin was analyzed by gel electrophoresis. Normal human liver ferritin was resolved into approximately six components with differing isoelectric points; these variants represent distinct molecular species. The fractionation of liver cell carcinoma ferritin revealed that some of the isoferritins were similar to those of normal liver; however, some of these tumor isoferritins had a more acidic isoelectric point. These tumor isoferritins were also demonstrable in early gestational fetal livers, but not in late gestational (eight months) or neonatal livers. HeLa ferritin resolved into two components, both with lower isoelectric points than any of the normal human ferritins. Early gestation placenta contained some isoferritins common to the liver, as well as two more acidic isoferritins which had the same pI and banded in the same positions as the HeLa isoferritins. Ferritins from normal and fetal livers and from hepatoma all contained only one, apparently identical, major subunit ranging in size from 18,000 to 19,000 daltons. In addition, different isoferritins from each tissue gave the same subunit species. However, analyses of the subunit patterns by electrophoresis at pH 3 in 6 M urea revealed two major subunit species in normal liver ferritin; subsequent examinations revealed that these two species were similar in size, but differed in surface charge. Double diffusion in agar gels revealed that normal and tumor ferritins share common antigenic determinants; normal human liver, hepatocellular carcinoma, and HeLa ferritins resulted in a precipitin line of complete identity. Thus, it appears that any quantitative differences in immunoprecipitability between HeLa and liver isoferritins must represent unreactive sites on both the isoferritins rather than an unreactive isoferritin species. The results demonstrate that ferritin undergoes a carcinofetal alteration in cancer tissue, and that human tumor cells may produce characteristic isoferritins which are not present in normal adult liver ferritin. The authors suggest that normal tissue ferritins are hybrid molecules consisting of different portions of at least two dissimilar subunits; the shift in isoferritin profiles in cancer cells may result from a synthesis of a unique subunit or by alterations in the proportions of two normal subunits.

3931 SIGNIFICANCE OF CELLULAR IMMUNOLOGY IN NEOPLASTIC DISEASES. (Pol.) Urasinski, I. (Klinika Hematologiczna Instytutu Chorob Wewn. PAM, ul. Unii Lubelskiej 71-344 Szczecin, Poland). *Wiad. Lek.* 28(8):653-656; 1975.

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3976 INFLUENCE OF METHYLPREDNISOLONE AND AZATHIOPRINE ON POLYMORPHONUCLEAR NEUTROPHILS (PMN) AND LYMPHOCYTES IN GERMFREE, MONOCONTAMINATED AND CONVENTIONAL RATS. (Eng.) Baardsen, A. (Kaptein Wilhelm Wilhelmsen og Frues Bakteriologiske Institutt, University Hospital, Rikshospitalet, Oslo, Norway); Midtvedt, T.; Trippestad, A. *Acta Pathol. Microbiol. Scand.* [*C*] 83(3):210-214; 1975.

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3978 LYMPHOCYTE POPULATIONS OF AKR/J MICE. III. CHANGES IN THE PRELEUKEMIC STATE. (Eng.) Zatz, M. M. (Natl. Cancer Inst., Immunology Branch, Bethesda, Md. 20014). *J. Immunol.* 115(4):1168-1170; 1975.

3979 EFFECT OF TUMOR ASCITIC FLUID ON LYMPHOCYTE TRAPPING AND MITOGEN RESPONSIVENESS OF LYMPH NODE CELLS [abstract] . (Eng.) Mongini, P. K. (Stanford Univ. Sch. Med., Calif.); Rosenberg, L. T. *Fed. Proc.* 34(3):1003; 1975.

3980 MODIFICATION BY HERPESVIRUS OF HEREDITARY GVHR COMPETENCY. (Eng.) Longenecker, B. M. (Medical Sciences Building, Univ. Alberta, Edmonton, Alberta T6G 2E1, Canada); Pazderka, F.; Ruth, R. F. *J. Immunogenet.* 2(1):59-64; 1975.

3981 EFFECT OF HYPOPHYSECTOMY ON THE DEVELOPMENT OF A T-CELL LEUKEMIA [abstract]. (Eng.) Bentley, H. P. (Kiwanis Club Cancer Cent., Univ. South Alabama, Mobile); Hughes, E. R.; Peterson, R. D. A. *Clin. Res.* 23(1):72A; 1975.

3982 ALTERATION OF T CELL FUNCTION IN HEALTHY PERSONS WITH A HISTORY OF THYMIC X-IRRADIATION. (Eng.) Rieger, C. H. L. (Dept. Pediatrics, P. O. Box 244, Univ. of Chicago, 950 E. 59th St., Chicago, Ill. 60637); Kraft, S. C.; Rothberg, R. M. *J. Allergy Clin. Immunol.* 56(4):273-281; 1975.

3983 TUMOR-DERIVED T CELL INHIBITORY PRINCIPLE [abstract]. (Eng.) Blom, D. H. (Dept. Med., Univ. Pennsylvania, Philadelphia); Brody, J. I. *Clin. Res.* 23(3):424A; 1975.

3984 CORRELATION OF EXPRESSION OF SURFACE MEMBRANE MARKERS WITH DIFFERENT STAGES OF B CELL DIFFERENTIATION IN MALIGNANT LYMPHOMAS IN MAN [abstract]. (Eng.) Augener, W. (Dept. Med., Univ. Essen, West Germany); Cohnen, G.; Brittinger, G. *Fed. Proc.* 34(3):842; 1975.

3985 SPONTANEOUS LYMPHOKINE SYNTHESIS BY HUMAN BLOOD MONONUCLEAR CELLS. (Eng.) Arvilommi, H. (Public Health Lab., SF-40620 Jyvaskyla 62, Finland); Rasanen, L. *Nature* 257(5522):144-146; 1975.

3986 AUGMENTED UPTAKE OF NEURAMINIDASE-TREATED SHEEP RED BLOOD CELLS: PARTICIPATION OF OPSONIC FACTORS. (Eng.) Schmidtke, J. R. (Dept. Surg., Univ. Minnesota, Box 306 Mayo, Minneapolis, Minn. 55455); Simmons, R. L. *J. Natl. Cancer Inst.* 54(6):1379-1384; 1975.

3987 SCANNING ELECTRON MICROSCOPY OF MURINE MACROPHAGES: SURFACE CHARACTERISTICS DURING MATURATION, ACTIVATION, AND PHAGOCYTOSIS. (Eng.) Polliack, A. (Hadassah University Hosp., Jerusalem, Israel); Gordon, S. *Lab. Invest.* 33(5):469-477; 1975.

3988 CONCANAVALIN A BINDING OF HUMAN COLON AND COLONIC TUMOR. (Eng.) Pittman, J. (Univ. Alabama Med. Cent., Birmingham, Ala.); Brattain, M. G.; Weiler, A.; Pretlow, T. G. II. *Fed. Proc.* 34(3):846; 1975.

See also:

* (Rev): 3615, 3616, 3617, 3619, 3623, 3647, 3650, 3651, 3652, 3653, 3654
* (Chem): 3712, 3768
* (Viral): 3807, 3808, 3811, 3837, 3858, 3874, 3878, 3882
* (Path): 4033, 4035, 4038, 4043, 4069

3989 FEULGEN-DNA-VALUES IN TRANSITIONAL CELL CARCINOMA OF THE HUMAN URINARY BLADDER. (Eng.) Fossa, S. D. (Norwegian Radium Hosp., Montebello, Oslo 3, Norway). *Beitr. Pathol.* 155(1):44-55; 1975.

Feulgen-stained imprint smears from 24 biopsy specimens from transitional cell carcinoma of the human urinary bladder were examined by means of scanning cytophotometry. One hundred randomly selected nuclei were measured from each biopsy specimen and the results compared with analogous measurements of nuclei from normal urinary transitional cell epithelium (13 cases in the control group). Of the nuclei in the control group 97% were diploid. Well differentiated transitional cell carcinoma of the bladder mainly had a diploid DNA-stemline comprising 85% or more of the cells. One case of a well differentiated bladder cancer with a tetraploid DNA-stemline was found. The different cases of moderately differentiated bladder cancer showed diploid, triploid, tetraploid and hexaploid DNA-stemlines, while four out of five poorly differentiated tumors had a diploid DNA-stemline. The fifth extremely de-differentiated bladder carcinoma did not have any DNA-stemline at all. Together with these changes of the ploidy of the DNA-stemlines, increasing undifferentiation of the tumor tissue was combined with a reduced number of cells belonging to the tumor DNA-stemline, and increasingly scattered distribution of cells not contributing to the DNA-stemline. This indicates increased proliferative activity and/or chromosomal instability of the poorly differentiated cell population. Predominance of cells in the diploid, tetraploid and or octoploid intervals without marked frequency of DNA-values in the intermediary classes may be a sign of clinically more "benign" bladder tumors, while a clinically more "malignant" tumor is characterized by increases of DNA-values in the triploid and hexaploid classes.

3990 EXPERIMENTAL BILHARZIAL SQUAMOUS METAPLASIA OF THE URINARY BLADDER IN HAMSTERS. (Eng.) El-Morsi, B. (Cancer Inst., Cairo Univ., Egypt); Sherif, M.; El-Raziki, E. S. *Eur. J. Cancer* 11(3):199-201; 1975.

An attempt was made to experimentally induce bilharzial squamous metaplasia in the urinary bladder of 8-wk-old hamsters. Cercariae of *Shistosoma haematobium* were obtained from naturally infected snails obtained from canals near Caire. Infection by total body immersion was repeated after three months. Seven to eleven months after first exposure, the animals were sacrificed and autopsied. Of the 16 hamsters surviving the test period, five showed no evidence of vesical schistosomiasis; 11 animals developed manifestations of schistosomal cytosis. Epithelial changes were detected in eight animals; hyperplasia was found in four and both hyperplasia and squamous metaplasia was detected in four. Two forms of squamous metaplasia were seen: one consisting of 12 or more layers of elongated basal cells with sharp margins and evident mitotic figures; the other resembling squamous metaplasia in man, and exhibiting all the structural layers of the epidermis. The development of squamous metaplasia is of particular interest, as it is considered to be a precancerous lesion.

3991 AUGMENTATION MAMMOPLASTY, IRRADIATION, AND BREAST CANCER: A CASE REPORT. (Eng.) Frantz, P. (Univ. North Carolina Sch. Medicine, Chapel Hill, N. C. 27514); Herbst*, C. A., Jr. *Cancer* 36(3): 1147-1150; 1975.

A case of a mammary adenocarcinoma associated with a left Cronin Silastic prosthesis in a 32-yr-old white woman is reported. Between the ages of 3-15 mo this patient had received six doses (quantity unknown) of irradiation to the left breast and back for two congenital hemangiomas. The lack of left-breast development and residual skin changes indicate that the irradiation exposure was significant. The prosthesis was implanted only two yr before the detection of cancer; it may have acted as a promoting factor. Study of this case indicates that: during mammoplasty, a random biopsy should be taken; all breast tissue should be placed superficial to the prosthesis to facilitate frequent examination; and open-excisional biopsy not violating the prosthetic pseudocapsule should be used to examine any mass. A standard radical mastectomy including removal of the pectoralis major and minor should be performed without violation of the pseudocapsule if a malignancy is found.

3992 MALE BREAST CANCER. (Eng.) Anonymous (No affiliation given). *Acta Pathol. Microbiol. Scand.* (Suppl. 251):13-35; 1975.

Male breast cancer was evaluated on the basis of data concerning 265 cases registered in Denmark over a period of 29 1/2 yr. The data were obtained by review of hospital records, survey of microscopic preparations, and examinations of surviving patients. The results are compared to results reported in the literature. Male breast cancer comprises 0.8% of all cases of breast cancer in Denmark. The average age at establishment of diagnosis was 65.2 yr in 257 cases. The duration of symptoms in breast cancer is considerably longer in males than in females, 16% having a duration of symptoms of two years or more. In only 13% was a palpable tumor the only symptom on admission. Twenty-seven percent had ulceration. Ulceration and fixation to the underlying tissue are not early symptoms in male breast cancer. According to the TNM classification, 35% of 253 cases were in clinical stage I, 11% in stage II, 42% in stage III, and 12% in stage IV. The clinical appearance of the disease showed a significant improvement from the period 1943-1957 to the period 1958-1972. This improvement is presumed to be related to the significant change in the clinical stage during the later period. The longer duration of symptoms in the male may give rise to the somewhat poorer prognosis in male breast cancer. Of the 265 cases, ten had a history of gynecomastia; this may support the theory that gynecomastia may be a premalignant state. Of 30 patients with breast cancer, one had the Klinefelter syndrome. By pooling series of male breast cancer, in which such screening has been made, it

was found that the incidence of the Klinefelter syndrome is higher among men with breast cancer than in the normal male population. Calculated on the basis of personal findings and the results reported by others, the incidence of breast cancer in Klinefelter patients was found to be about 20 times higher than in normal men and about one-fifth of the incidence in females. Men with breast cancer had no specific metabolism of iv administered estradiol-17β or a specific urinary excretion of hormones in this series. However, 25 patients did excrete a significantly smaller quantity of pituitary gonadotrophins than did a control group comprising 60 healthy men of comparable age. The observed and corrected 5-yr survival rates for this disease were 36% and 46%, respectively. The findings in this and other studies give no indication that radical mastectomy is to be preferred to simple mastectomy, since the latter gives rise to fewer postoperative complications and is less strenuous. Therefore, simple mastectomy is recommended for these patients, 40% of whom are 70 yr or more. It is also recommended that the treatment of this rare disease be centralized as much as possible.

3993 INAPPROPRIATE PRODUCTION OF COLLAGEN AND PROLYL HYDROXYLASE BY HUMAN BREAST CANCER CELLS *IN VIVO*. (Eng.) Al-Adnani, M. S. (Univ. Dept. Pathology, Royal Infirmary, Glasgow, Scotland); Kirrane, J. A.; McGee*, J. O. *Br. J. Cancer* 31(6):653-660; 1975.

Thirty-two scirrhous cancers of breast were examined to determine the origin of the collagen stroma in these tumors. The capacity of normal, nonneoplastic, and neoplastic breast epithelium to synthesize collagen was identified by immunoperoxidase procedure and by an immunoglobulin-enzyme-bridge method, using antibodies to collagen and to prolyl hydroxylase. The malignant epithelial cells in 30 of the tumor tissues contained not only collagen, but also prolyl hydroxylase. Neither this collagen-biosynthetic enzyme nor collagen itself was detectable in the spindle cells in the stroma of the tumors. Neither the epithelium in normal breast, that in fibrocystic disease and in fibroadenomata, nor the malignant epithelium in two medullary cancers of breast contained either collagen or prolyl hydroxylase. These results strongly suggest that the malignant epithelium of scirrhous breast cancers produces its own collagen stroma, and that the scirrhous reaction in these tumors is not a host response to tumor invasion. The production of collagen and prolyl hydroxylase by breast cancer cells (of the scirrhous type) therefore represents another example of inappropriate protein production by a human tumor.

3994 FINE STRUCTURE OF A CEREBELLAR "FIBROMA". (Eng.) Hirano, A. (Montefiore Hosp. and Medical Center, 111 East 210 St., Bronx, N.Y. 10461); Llena, J. F.; Chung, H. D. *Acta Neuropathol. (Berl.)* 32(3):175-186; 1975.

The fine structure of an intracerebellar "fibroma" was examined. The golf ball-sized tumor was totally removed from the left cerebellar hemisphere of a 19-yr-old man. It was not attached to the dura mater and was encapsulated. A portion was examined with the electron microscope. The tumor consisted of irregularly-shaped cells connected by well developed junctional complexes. Unusual, fenestrated capillaries with extremely narrow and irregular lumens were frequent. Collagen fibers were uncommon, but the wide extracellular spaces contained large amounts of dense, granular or fibrillar material. The dense material coated the tumor cells and was apparently secreted from small vesicles found within these cells. This tumor is compared with other previously reported tumors with similar characteristics.

3995 NERVOUS SYSTEM NEOPLASMS AND PRIMARY MALIGNANCIES OF OTHER SITES: THE UNIQUE ASSOCIATION BETWEEN MENINGIOMAS AND BREAST CANCER. (Eng.) Schoenberg, B. S. (Section Publications, Mayo Clinic, 200 First St., S.W., Rochester, Minn. 55901); Christine, B. W.; Whisnant, J. P. *Neurology* 25(8)705-712; 1975.

To determine whether nervous system neoplasms are associated with primary malignancies elsewhere, the frequency of multiple primary tumors in patients in whom at least one of the primary tumors was within the nervous system was studied. The patients were Connecticut residents with tumors diagnosed between 1935 and 1964. Of 135 patients, 130 had two primary tumors, four had three primary tumors, and one had four primary tumors. Only with multiple primary tumors involving the brain and breast did the number of observed cases significantly exceed the number of expected cases; eight patients who had a meningioma associated with a breast cancer accounted for this excess. Patients with breast cancer presenting with signs or symptoms of an intracranial neoplasm should be carefully evaluated as the intracranial lesion may be a potentially curable meningioma.

3996 CYTOPHOTOMETRICALLY DETERMINED DNA-PATTERN OF PREMALIGNANT CASES OF DYSPLASIA OF THE CERVIX UTERI: CONTRIBUTION TO THE PROBLEM OF MORPHOLOGIC DEFINITION AND CLINICAL SIGNIFICANCE OF THESE LESIONS. (Ger.) Sachs, H. (Universitäts-Frauenklinik D-6650 Homburg/Saar Bundesrepublik Deutschland); Schittko, G. *Arch. Gynaekol.* 218 (2):95-112; 1975.

Tissue samples from 12 cases of possibly benign epithelial lesions of the uterine neck (metaplasia, regenerating epithelium, atrophic and parakeratotic epithelium, basal cell hyperplasia, and epithelium irritated by inflammation), as well as from eight cases of slight to serious epithelial dysplasia, and from four cases of carcinoma *in situ* were analyzed cytophotometrically. Samples from benign epithelial lesions had a normal DNA pattern. Premalignant dysplasias of all stages showed, however, an aneuploid DNA content in all cases. There was no diploid mode, and atypical proliferation with polydiploidization, DNA stem lines, and a broad scattering of the DNA levels were the characteristic features of premalignant dysplasia and of carcinoma *in situ*. More or less extended loss of the epithelial stratification,

considerable disturbances in differentiation, pronounced individual polymorphism of cells and nuclei, and hyperchromasia of the nuclei were observed. These data confirm the hypothesis that premalignant dyplasia assumes an intermediate position between normal cervical epithelium and carcinoma *in situ*.

3997 *IN-SITU* AND MICROINVASIVE ADENOCARCINOMA OF THE UTERINE CERVIX: A CLINICAL, CYTOLOGIC AND HISTOLOGIC STUDY OF 14 CASES. (Eng.) Qizilbash, A. H. (Henderson Gen. Hosp., Hamilton, Ontario, Canada). *Am. J. Clin. Pathol.* 64(2):155-170; 1975.

The clinicopathologic features of 14 cases of *in situ* and microinvasive adenocarcinoma of the cervix, encountered during 1961-1974, are reported. Seven cases represent examples of *in situ* and seven, microinvasive adenocarcinoma. In two cases, microinvasive adenocarcinoma was the only lesion found on histologic examination. Severe dysplasia and carcinoma *in situ* of the squamous epithelium were coincidental findings in 12 patients. Papanicolaou smears were abnormal in all 14 patients. In nine, malignant glandular cells were identified. Five smears contained both malignant squamous and glandular cells. The mean age of the 14 patients was 38.4 yr. Thirteen patients had borne one to six children. Two were pregnant at the time of diagnosis, and four were on birth control medication. Thirteen of the patients underwent conization biopsy. Hysterectomy in one form or another was curative in all. The relatively infrequent occurrence of *in situ* adenocarcinoma is probably due to the low incidence of cervical adenocarcinoma and to the fact that the lesion is focal and easily overlooked. Five of the cases in the present series were a chance finding in a review of 200 consecutive cone biopsies of the cervix. The *in situ* lesion is histologically similar to the microinvasive adenocarcinoma; both lesions resemble the well-differentiated type of invasive adenocarcinoma. Similar *in situ* changes confined to glands at the periphery of the invasive foci were seen, suggesting progression of the *in situ* lesion to invasive cancer.

3998 COLLAGENASE ACTIVITY IN EPIDERMOID CARCINOMA OF THE ORAL CAVITY AND LARYNX. (Eng.) Abramson, M. (Dep. Otolaryngol. Maxillofac. Surg., Univ. Iowa, Iowa City); Schilling, R. W.; Huang, C.; Salome, R. G. *Ann. Otol. Rhinol. Laryngol.* 84(2/Part 1):158-163; 1975.

A study was conducted to examine collagenase activity in head and neck carcinomas of two sites, and to determine if the amount of collagenase activity could be correlated with the clinical behavior of the disease. Biopsy specimens of epidermoid carcinomas and uninvolved mucosa from the oral cavity, hypopharynx and larynx were obtained at the time of diagnostic biopsy of definitive excisions. A series of 14 epidermoid carcinomas produced a collagen-dissolving enzyme *in vitro* as demonstrated by the breakdown of ^{14}C-labeled collagen. Oral cavity tumors showed greater activity than laryngeal carcinomas, while both sites were more active than uninvolved mucosa from the same patients. Tumor-associated collagenase activity, in common with previously described collagenases, could only be demonstrated *in vitro* and required protein synthesis. Maximum tumor collagenase occurred at 24 hr *in vitro* and then declined as compared with the maximum collagenase at 72 hr *in vitro* produced by oral cavity mucosa. The 14 patients in the series were ranked in order of the collagenase activity of their tumors. At 18 mo after the diagnosis, 4 of the 6 patients with the most active tumors were dead of cancer, and one patient was alive with persistent cancer. High collagenase activity may be a factor in the clinical aggressiveness of epidermoid carcinomas of the head and neck.

3999 CARCINOMA *IN SITU* OF THE LARYNX. (Eng.) Holinger, P. H. (700 North Michigan, Chicago, Ill. 60611); Schild, J. A. *Laryngoscope* 85(10):1707-1708; 1975.

To provide a clinical evaluation of the management of keratosis, keratosis with atypia, and carcinoma *in situ* with or without microinvasion, 23 patients "in the all inclusive category of carcinoma *in situ*" of the larynx were studied. The results indicate that carcinoma *in situ* should be treated with a full course of radiation or "adequate excisional surgery". No conclusions on the benign or malignant potential of keratosis and carcinoma *in situ* can be drawn from the information available.

4000 BENIGN SMOOTH MUSCLE TUMOURS. (Eng.) Farman, A. G. (Dept. Oral Pathology, Univ. Stellenbosch, Parowvallei, CP South Africa). *S. Afr. Med. J.* 49(33):1333-1340; 1975.

A series of 7748 benign smooth muscle tumors, diagnosed in South Africa during a period of 24.5 yr, is presented. Ninety-five percent of these leiomyomas occurred in the female genital tract; in another 61 cases there was inadequate histologic material or uncertainty about the site of origin. The remaining 310 lesions were analyzed for histologic, sex, race, site, and age distributions. There were 230 skin lesions, 42 stomach lesions, 18 small intestinal and duodenal lesions, 7 esophageal lesions, 5 oral lesions, 5 bladder lesions, and 4 lesions of the large intestine. The larynx, kidney, and liver were each involved once. Males were affected in 138 instances and females in 161. The lesions tended to occur slightly earlier in black than in white females. Simple leiomyomas comprised 201 (65%) of the lesions, angiomyomas 91 (29%), and epithelioid leiomyomas 18 (6%). Comparisons were made between the skin, gastric, and oral lesions. Of the five oral cases, four were angiomyomas and none was a simple leiomyoma. In contrast, simple leiomyomas accounted for 83% of the stomach lesions and 62% of the skin lesions. Only 7% of the gastric lesions were angiomyomas compared with 34% of the skin lesions. Although there was no significant variation of age distribution between simple leiomyomas and angiomyomas, the cutaneous simple leiomyomas occurred in a slightly younger age group than did the angiomyomas. The data show that smooth muscle tumors may occur at any site where smooth muscle is present. Angiomyomas, rather than simple leiomyomas, are more

likely to occur in regions where smooth muscle is found mainly in blood vessels. Simple leiomyomas predominate in the stomach, which is a hollow viscus filled with a band of smooth muscle.

4001 SUPPURATIVE MIXED TUMOR OF THE PHARYNX. (Rus.) Parkhomovskii, M. A. (Dept. Otorhinolaryngology, MSCh No. 61, Moscow, U.S.S.R.). *Zh. Ushn. Nos. Gorl. Bolezn.* (1):105-106; 1975.

Suppurative mixed tumor of the pharynx was removed from a 58-yr-old man. The tumor was originally diagnosed as a suppurative cyst. It was composed of cartilage with a pus-containing central cavity. Histological examinations revealed chronic tonsillitis and chronic inflammation of the paratonsillar tissues. The patient had undergone ophthalmectomy for a sarcoma about 20 yr previously. He is free from recurrence for over five years despite incomplete excision of the tumor capsule.

4002 ULTRASTRUCTURE OF ANAPLASTIC (SPINDLE AND GIANT CELL) CARCINOMA OF THE THYROID. (Eng.) Jao, W. (Michael Reese Medical Center, Chicago, Ill. 60616); Gould, V. E. *Cancer* 35(5):1280-1292; 1975.

Three anaplastic (spindle and giant cell) carcinomas of the thyroid were studied by light and electron microscopy; two of the tumors also included foci of recognizable follicular carcinoma. The patients were women, 66-71 yr old. The follicular carcinoma cells displayed prominent mitochondria and rough endoplasmic reticulum, and showed evidence of secretory activity. Desmosomes and complex cellular interdigitations were evident. Basal laminae were present, with conspicuous reduplication in the well-differentiated foci. However, some epithelial clusters were surrounded by basal lamina, showing focal discontinuities through which epithelial cells protruded into the stroma. The pleomorphic spindle and giant cells showed cytoplasmic and nuclear characteristics similar to the better differentiated carcinomatous follicular elements, but showed rare desmosomes and no basal laminae. The basic ultrastructural similarity between follicular and anaplastic tumor cells confirms their common epithelial origin. However, while partially retaining their secretory capability, the anaplastic cells progressively lose their capacity to synthesize basal lamina and develop complex cellular attachments.

4003 FINE STRUCTURE OF A RADIATION-INDUCED OSTEOGENIC SARCOMA. (Eng.) Lee, W. R. (Western Infirmary, Glasgow, Scotland); Laurie, J.; Townsend, A. L. *Cancer* 36(4):1414-1425; 1975.

An osteogenic sarcoma arose in the right orbit of a seven-yr-old boy five yr after the right orbit had been treated by four courses of radiotherapy (total dose approximately 13,000 rads) for a multicentric retinoblastoma. Death occurred six months after the orbital tumor was first detected. Study of the tumor by electron microscopy showed a varied morphology of cells in which two main types were identified. In one group, the cells were large with radiolucent cytoplasm, which contained long branching segments of rough endoplasmic reticulum. In the second group, the cells were smaller with irregular nuclei and an electron-dense cytoplasm, which contained short segments of dilated rough endoplasmic reticulum and numerous mitochondria. The first group of cells closely resembled osteoblasts, while the second group had some features of osteoclasts or their precursors. Phagocytosis occurred within many of the tumor cells. The branching processes of the tumor cells were separated by an amorphous ground substance, which contained collagen-like fibrils and hydroxyapatite crystals. Crystal deposition was in some instances in close relation to extracellular membrane-bound vesicles.

4004 XC-CELL FUSION INDUCED BY MURINE PLASMOCYTOMA CELLS: II. CYTOLOGICAL AND ULTRASTRUCTURAL STUDY. (Eng.) Lemay, P. (U 102, INSERM, 2, place de Verdun, 59045 Lille, France); Torpier, G.; Lefebvre, J. C.; Samaille, J. *Biomedicine* 23(5):168-175; 1975.

The kinetics and morphologic aspects of XC cell syncytium formation induced by MF_2 cells, a mouse plasmocytoma-derived cell line, were studied. The MF_2 cells (3×10^3) and the XC cells (25×10^3) were cocultured for 18 hr in each well of a Microtest II tissue culture plate. Only one MF_2 nucleus was shown to be included in one syncytium by autoradiographic and optical microscopic methods. A partial inhibition of syncytium formation, either in number or in size, could be obtained with actinomycin D (1 μg/ml) added to one or the other cell line, and to a lesser extent by preincubation of MF_2 cells with cycloheximide (10 μg/ml). Pretreatment of either cell line with hydroxyurea (5 mM) did not inhibit syncytium formation. These results suggested that a normal RNA synthesis was required to obtain optimal polykaryon growth. The reduced size of syncytia observed after pretreatment of MF_2 cells with either actinomycin D or cycloheximide may have resulted from a reduction in the number of C-type particles visible in the electron microscope; these particles could represent sites for polykaryon induction. Immunoelectron microscopy using a syngeneic mouse MF_2 cell antiserum and peroxidase labeling revealed a complete mixing and redistribution of the respective plasma membrane sites of MF_2 and XC cells on the polykaryon surface. The dilution of the MF_2 cell membrane sites on the syncytium surface is discussed in relation to the possible role of virus particles in the fusion process. Progressive dilution of budding virus sites would influence the size of the polykaryon; a minimal density of budding sites/cell surface unit would therefore be required to induce or allow the development of a polykaryon. Experiments to elucidate this point are in progress.

4005 FENESTRAE IN GOLGI AND ENDOPLASMIC RETICULUM CISTERNAE OF HUMAN BRAIN TUMOURS. (Eng.) Tani, E. (Hyogo Coll. Med., Japan); Ametani, T.; Nakano, K.; Nishiura, M.; Higashi, N. *Acta Neuropathol. (Berl.)* 31(1):13-19; 1975.

Fenestrae were demonstrated by electron microscopy in cisternae of the Golgi apparatus and endoplasmic reticulum (ER) of 27 human brain tumors. Specimens included six glioblastomas, three oligodendrogliomas, two ependymomas, three medulloblastomas, one medulloepithelioma, five meningiomas, one cerebellar sarcoma, three hemangioblastomas, and three chromophobe adenomas. The cisternae were freeze-fractured and surfaces of the specimens were replicated by platinum and carbon. Fenestrae appeared as conical protrusions or circular broken-off necks on fracture face A and as circular holes on face B of Golgi and ER membranes in tangential fractures. (Face A directs towards the luminal cisternae while face B directs towards the cytoplasmic matrix.) In Golgi cisternae, fenestrae were 200-400 A in diameter and often diffusely distributed or concentrated in groups. In ER membrane they were 300-600 A and scattered. Smaller fenestrae appeared morphologically different from larger ones. In transverse fractures, the fenestrae appeared as several constrictions of the cisternae. Ellipsoidal protrusions, about 150 x 100 A, were sometimes visible on face B of ER cisternae. The significance of the fenestrae is unknown, but they would provide a wider range of functional capabilities than the classical sac-like cisternae.

006 THE FINE STRUCTURE OF HYALINE INCLUSIONS (PSEUDOPSAMMOMA BODIES) IN MENINGIOMAS. (Eng.) Kepes, J. J. (Univ. Kansas Med. Cent., Kansas City). *J. Neuropathol. Exp. Neurol.* 34(3):282-289; 1975.

Hyaline inclusions contained in a convexity meningioma excised from the right frontal lobe of a 69-yr-old man were studied by electron microscopy. By light microscopy, sections of the tumor stained with hematoxylin and eosin showed a meningothelial meningioma with numerous cellular whorls, some of which had undergone hyalinization and others early calcification. Numerous hyaline inclusions were found throughout the tumor; the smaller ones appeared to be intracellular, the larger ones extracellular. The intracellular inclusions, particularly, were similar to eosiniphilic hyaline globules seen in other neoplasms. By electron microscopy the inclusions were seen both individually and in clusters. They were composed of moderately electron dense material, mostly finely granular in nature. The larger inclusions were located extracellularly and were surrounded by one or more meningiothelial cells. In the interphase between cells and hyaline bodies the cell membranes displayed numerous microvilli. Material morphologically similar to the granules was observed on the inner side of the cell membrane, as well as within the microvilli. Hyaline inclusions contained within cells also occupied a space lined by microvilli. Some cells contained more than one inclusion. Because of the presence of proteinaceous material in the microvilli-lined extracellular spaces, and because of the presence of intracellular spaces, also lined by microvilli and filled with proteinaceous inclusions, meningioma with secretory differentiation may be another histological variation of meningioma. The presence of hyaline inclusions may be regarded as a possible factor in ultrastructural differential diagnosis between meningiomas and gliomas.

4007 THE ULTRASTRUCTURAL IDENTIFICATION OF TISSUE BASOPHILS AND MAST CELLS IN HODGKIN'S DISEASE. (Eng.) Parmley, R. T. (Med. Univ. South Carolina, Charleston); Spicer, S. S.; Wright, N. J. *Lab. Invest.* 32(4):469-475; 1975.

Mast cells and basophils, (numbering 2-10 cells per high power microscopic field) are described in tumor stroma of patients with untreated Hodgkin's disease. A tumorous splenic lymph node taken from one to ten patients contained both cell types. Mast cells alone were found in large numbers in the pulmonary tumor of another patient and smaller numbers were found in tumors of five additional patients. Electron microscopy revealed that the basophils resembled peripheral blood basophils. They contained caveolae and large round granules that often contained uniform intragranular particles and myelin figures. The tumor mast cells showed a prominent Golgi apparatus and contained numerous granules which varied in density and in particle content. They occasionally showed protruding granules indicating exocytosis, and caveolae suggesting pinocytosis. Some cells had a subsurface lacunar system. Mast cells found in reduced numbers in tumor-free lymph nodes of two other patients contained comparatively more closely packed and structurally uniform granules than tumor mast cells. They contained more lipid droplets, showed no evidence of pinocytosis or exocytosis, and they lacked lacunar systems. These differences suggest that mast cells, and occasionally basophils infiltrating tumor tissue, are activated by Hodgkin's disease. Through exocytosis, they evidently play a role in the inflammatory response of the disease and may mediate immunologic reactions.

4008 THE ULTRASTRUCTURE OF MOUSE NEUROBLASTOMA CELLS IN TISSUE CULTURE. (Eng.) Ross, J. (Dep. Biol., Yale Univ., New Haven, Conn.); Olmstead, J. B.; Rosenbaum, J. L. *Tissue Cell* 7(1):107-136; 1975.

The different morphological forms of cultured neuroblastoma cells were studied by light and electron microscopy. A clonal cell line from a murine sympathetic ganglion tumor was grown in suspension or monolayer cultures to produce round cells without neurites or extended cells with neurites, resp. Some monolayer cultures were grown in hypertonic medium containing 0.18 M sucrose or 0.2 M NaCl to produce superdifferentiated forms. Cells for light microscopy were grown on coverslips; those for electron microscopy were fixed in glutaraldehyde, post-fixed in OsO_4, and stained with uranyl acetate and lead citrate. Light microscopy showed the cells grown in suspension to be spheroid and about 20-40 μ in diameter with thin undifferentiated cytoplasmic processes about 5-10 μ in length. Those grown in monolayers were diverse in form with 80-90% having developed neurites within 24 hr. Some were round and about 30-60 μ in diameter, while others were flattened and about 200 μ in diameter. Neurites varied in number, length, diameter, and arborization. One to several were present per cell,

and were diversified along their length. When cells reached confluency, they became more homogeneous. The cells grown in hypertonic medium developed longer, more differentiated neurites than normal. Electron microscopy showed the round-type cells had normal organelles, microtubules, and sparse numbers of filaments randomly distributed throughout the cytoplasm without orientation. Virus-like particles were a prominent feature. They were doughnut-shaped or round dense structures about 700-800 Å in diameter. The extended monolayer cells were similar but contained vesicles and neurofilaments typical of normal neurons. Some vesicles were coated with clear centers or dense cores, or had dense cores bounded by smooth membrane. The first type were 1,000-5,000 Å in diameter with radiating T-shaped striae, 150-200 Å long, and were frequently associated with the cell membrane. The last type were about 1,500-2,500 Å in diameter and were frequently clustered. They occasionally had striae. Filaments similar to normal neurofilaments, 90-100 Å in diameter, were found in the neurites and perikaryon. Occasionally they were grouped into bundles. Individual filaments had a periodicity of about 100 Å. Virus-like particles were scattered through the cytoplasm, sometimes occurring in large clumps. They were usually within smooth endoplasmic reticulum cisternae. Cell junctions consisted of two apposed membranes with a gap of 200 Å and a dense fuzzy material in the cytoplasm on either side. The hypertonic cells had clusters of spherical vesicles like those of cholinergic neurons; they were seen close to neurite contact points, along the length of the neurite, and in the cell bodies. It is concluded that neuroblastoma lines may form functional junctions with other cells.

4009 ULTRASTRUCTURE OF THE SINUS WALL OF MURINE BONE MARROW IN MYELOGENOUS LEUKEMIA. (Eng.) Campbell, F. (Health Sci. Cent., Univ. Louisville, Ky.); *Am. J. Anat.* 142(3):319-333; 1975.

The bone marrow ultrastructure of six male RD mice iv injected with 2 x 10^6 leukemic myelocytes was investigated to determine if alterations occur in the sinus wall. Bone marrow fixative was perfused *via* the vascular system 25 days after inoculation, and sections were embedded in plastic for electron microscopy. Leukemic bone marrow sinuses appeared normal in size, shape and frequency of occurrence. The number of lining cells of the sinus wall appeared normal, and they had organelles similar in distribution and number to those of normal lining cells. The sinus wall was continuous, having openings (0.3-3 μ) only in conjunction with blood cells that were migrating through. These migration pores occurred within, and not between, lining cells. These similarities of leukemic sinuses to normal sinuses indicated that the ability of leukemic cells to pass through lining cells was not due to abnormal migration pores. Adventitial cells were markedly less numerous in leukemic marrow and exhibited degeneration. An increase in thickness and an abnormal distribution of extracellular material near the basal surface of leukemic lining cells were observed. This material was not present near migration pores, and the possibility that it interfered with pore formation is suggested. Filaments 100 A in diameter associated with the substance suggested a chemical composition different from normal basal lamina. Virus-like particles were aggregated on the endoplasmic reticulum and in the leukemic cell cytoplasm, and particles 300-500 A in diameter were seen in the extracellular space. The large number of these particles suggests their involvement in or association with the leukemic state.

4010 COMPARATIVE ELECTRON-MICROSCOPIC FEATURES OF NORMAL, HYPERPLASTIC, AND ADENOMATOUS HUMAN COLONIC EPITHELIUM. II. VARIATIONS IN SURFACE ARCHITECTURE FOUND BY SCANNING ELECTRON MICROSCOPY. (Eng.) Fenoglio, C. M. (Coll. Physicians and Surgeons of Columbia Univ., 630 West 168 St., New York, N.Y. 10032); Richart, R. M.; Kaye, G. I. *Gastroenterology* 69(1):100-109; 1975.

The high resolution and the great depth of focus possible with the scanning electron microscope aided in defining the surface features of normal human colonic mucosa and the mucosa of human colonic polyps. Thirteen hyperplastic polyps and 15 adenomas were obtained at sigmoidoscopy, clectomy, or polypectomy or from colons resected for carcinoma. Specimens were dehydrated with a graded series of ethanol solutions, and infiltrated with a graded series of ethanol-amyl acetate solutions before critical point drying from liquid CO_2; they were then coated with gold-palladium and examined with the scanning electron microscope. Sections were also examined histologically. This technique demonstrated that the surface of the normal colon has a territorialization that encompasses multiple crypts. The surface of the normal colon was covered with both absorptive cells and goblet cells. Hyperplastic polyps were covered with overdeveloped absorptive cells, and the normal territorialization was present but was distorted. Adenomatous polyps were covered with immature cells and, except for the villous adenomas, goblet cells were absent from the surface. The territorial patterns were totally obliterated in the adenomas. The results confirm the existence of divergent patterns of surface morphology in hyperplastic and adenomatous mucosa corresponding to the divergent cytological patterns that have been previously described from histological, autoradiographic, and transmission electron microscopic studies.

4011 BURKITT'S LYMPHOMA PRESENTING AS ACUTE LEUKAEMIA. (Eng.) Jaiyesimi, F. (Univ. Coll. Hosp., Ibadan, Nigeria); Oluboyede, O.; Taylor, D.; Familusi, J. B. *Acta Haematol. (Basel)* 54(2):115-119; 1975.

An 8-yr-old Nigerian boy presented with extensive superficial lymphadenopathy, a bleeding diathesis, and numerous tumor cells in blood and bone marrow. Further characterization of the tumor cells confirmed the diagnosis of Burkitt's lymphoma. Peripheral blood film showed numerous blast cells (10-15 μm in diameter) with multiple cytoplasmic vacuolations and 2-3 nucleoli in each nucleus. Iliac bone marrow aspiration revealed complete bone marrow replacement by Burkitt's lymphoma cells morphologically identical

to those in the peripheral blood. Methylgreen-pyronine staining of the bone marrow aspirate indicated intense pyroninophilia of the cytoplasm of all blast cells, a characteristic feature of Burkitt's lymphoma. Phase contrast cytology of peripheral blood cells showed blast cells with scanty cytoplasm containing conspicuous lipid granules. The patient died four days after admission. It is suggested that the poor prognosis in children with Burkitt's tumor and bone marrow involvement may be due to a deficiency in immunological competence. Antibody titers to viral capsid antigens of Epstein-Barr virus were significantly lower in this patient than those reported in a previous study of African children with Burkitt's lymphoma.

4012 MYXOVIRUS-LIKE PARTICLES IN CELLS OF AMERICAN BURKITT'S-TYPE LYMPHOMA. (Eng.) Popoff, N. A. (Jackson Memorial Hosp., 1700 N.W. Tenth Ave., Miami, Fla. 33152); Malinin, T. I. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6:47-52; 1975.

A labial lesion in a 16-mo-old white girl was diagnosed as American Burkitt's-type lymphoma. A late relapse with CNS involvement occurred five mo after onset of the disease and radio- and chemotherapy. Ultrastructural studies of the primary tumor revealed well-preserved neoplastic lymphoid cells containing distinct tubular arrays in intimate association with cisternae of endoplasmic reticulum. Microscopically, lymphomatous infiltration of the meninges was present throughout the cerebrum, brain stem, and cerebellum; the infiltrates extended along the peripheral portion of the cranial nerves and obliterated most of the perivascular spaces. Phagocytic reticuloendothelial cells containing ingested neoplastic cells and cellular debris were invariably present in the infiltrates. CNS involvement during a late relapse of Burkitt's lymphoma may be the result of tumor reinduction impelled by the same agent that induced the primary tumor. Although cytochemical analysis of the tubular arrays did not demonstrate nucleic acids, their viral origin cannot be ruled out. The tubular arrays may represent incomplete forms of a latent virus, and thus stimuli responsible for cell proliferation may also lead to increased production of the particles. Alternatively, the tubular structures may be related to immunoglobulin production and therefore to an enhancement of phagocytosis.

4013 AMERICAN BURKITT'S LYMPHOMA: A CLINICO-PATHOLOGIC STUDY OF 30 CASES. I. CLINICAL FACTORS RELATING TO PROLONGED SURVIVAL. (Eng.) Arseneau, J. C. (Natl. Cancer Inst., Bethesda, Md.); Canellos, G. P., Banks, P. M.; Berard, C. W.; Gralnick, H. R.; DeVita, V. T., Jr. *Am. J. Med.* 58(3): 314-321; 1975.

Thirty cases of American Burkitt's lymphoma and the results of therapy are described. Median age of the patients was 11 yr. Five patients presented with localized disease. The abdomen was the most frequent site of involvement (19 cases). There was a high correlation between serum lactic acid dehydrogenase (LDH) levels and stage of the disease; lowest levels correlated with localized disease, whereas higher LDH levels corresponded to wide dissemination and/or large abdominal tumors. Of 22 patients receiving parenteral cyclophosphamide as the primary mode of therapy, complete remissions were obtained in 59%; four of these relapsed and three died of the recurrent tumor. The tumor recurred at the initial tumor site in 3 of the 4 patients who relapsed. Metabolic complications attributed to chemotherapy, which developed in 27% of the patients, appeared related to the mass of tumor present and to rapid and massive lysis of the malignant cells; such consequences included primarily hyperkalemia (six cases), hypocalcemia, hyperphosphatemia (one case), and lactic acidosis (one case). There were four sudden deaths within 48 hr of therapy. Of the seven patients receiving radiation therapy and/or chemotherapy other than cyclophosphamide, none survived longer than six months. Survival was correlated with the clinical stage of the disease, with a median survival of seven months for all patients in the survey. The site and volume of tumor mass predicted for prolonged survival. None of the six patients with bone marrow or CNS involvement remained tumor-free. The greater frequency of abdominal disease reported in American Burkitt's lymphoma, as opposed to the frequent localized jaw tumors of East African patients was noted and a host reaction against the lymphoma is suspected. The author also suggests that the very high growth fraction of Burkitt's lymphoma may explain its marked sensitivity to chemotherapy. Sixty percent of patients presenting only jaw tumor remained alive and free of disease. The median survival of those presenting abdominal tumor was seven months; patients experiencing CNS and bone marrow involvement survived an average of two months after diagnosis.

4014 BURKITT LYMPHOMA IN THREE AMERICAN CHILDREN: CLINICAL AND CYTOGENETIC OBSERVATIONS. (Eng.) Hubner, K. F. (Div. Medical and Health Sciences, Oak Ridge Associated Univ., PO Box 117, Oak Ridge, Tenn. 37830); Littlefield, L. G. *Am. J. Dis. Child.* 129(10);1219-1223; 1975.

The clinicopathological observations of three American children with Burkitt's lymphoma are presented and cytogenetic findings of two of the cases are described. A 9-yr-old boy developed a small painless lump on the right side of the neck that continued to grow despite penicillin treatment. The lump was partially excised and appeared microscopically as lymphoblastic lymphoma. WBC count revealed no abnormalities except for lymphopenia. Neoplasm scanning showed abnormal uptake of the radioactive nuclide on the right side of the neck and around the pancreas. Laparotomy revealed a neoplasm involving the pancreas. The histological diagnosis was malignant lymphoma of the lymphoblastic type, consistent with Burkitt's lymphoma. A 15-yr-old girl presented with generalized urticaria, anorexia, nausea, vomiting, weight loss, and dyspnea. Left inguinal lymph node biopsy and a bone marrow smear disclosed a malignant lymphoma of the poorly differentiated lympho-

cytic type with starry sky pattern, Burkitt type. The patient had visible nodular swellings in the cervical and supraclavicular regions bilaterally, and enlarged lymph nodes. The third case, a 4 1/2-yr-old boy, developed symptoms of partial gastrointestinal obstruction. Exploratory laparotomy revealed a 475 g retrocecal neoplasm involving the entire ascending colon. Histological diagnosis was malignant lymphoma, poorly differentiated, lymphocytic type, involving the colon and adjacent structures. Hematological evaluations of bone marrow smears from cases 2 and 3 showed a massive infiltration of lymphoma cells into the marrow at various times during the course of the illness. Because of the variability of clinical manifestations of presenting symptoms, early diagnosis and treatment of Burkitt's lymphoma may be delayed. The prognosis is poor in advanced cases, especially where there is CNS or bone marrow involvement.

4015 ABDOMINAL LYMPHOMA WITH α-HEAVY CHAIN DISEASE. (Eng.) Plesnicar, S. (Fac. Medicine, Inst. Oncology, Ljubljana, Yugoslavia); Sumi-Kriznik, T.; Golouh, R. *Isr. J. Med. Sci.* 11(8):832-837; 1975.

The case of a 27-yr-old man with abdominal lymphoma is presented. Clinical, immunochemical and pathological studies were performed when the patient presented with abdominal pain, the malabsorption syndrome and marked weight loss. The concentration of IgA, as measured by a radial diffusion method, was elevated (860-3,080 mg/100 ml). Immunoelectrophoretic studies revealed α-heavy chains in the patient's serum, urine and intestinal juice. Treatment with cyclophosphamide and corticosteroids produced an improvement in the patient's condition and he survived for 18 mo after the onset of symptoms. Autopsy revealed a malignant lymphoma of mixed histiocytic-lymphocytic type involving mainly the mesenteric lymph nodes, but also affecting the jejunal mucosa, liver, spleen and extraabdominal lymph nodes. This is the first case of abdominal lymphoma with α-heavy chain disease to be reported from Yugoslavia.

4016 TUMOUR ANGIOGENIC FACTOR ASSOCIATED WITH SUBCUTANEOUS LYMPHOMA. (Eng.) Wolf, J. E. (Baylor Coll. Med., Houston, Tex.); Hubler, W. R., Jr. *Br. J. Dermatol.* 92(3):273-277; 1975.

In order to test for the presence of a diffusable Tumor Angiogenic Factor (TAF), 2.0 mm fragments of a subcutaneous lymphoma from the forehead of a 4-yr-old Oriental-American girl were implanted in hamsters. The fragments were implanted in direct aposition to the vascular membrane of the cheek pouch membrane of six hamsters or separated from the cheek pouch vascular bed by 6.0 mm discs of millipore filter (type TA, 0.45 μm pore size, 25 μm thick) in another six hamsters. Implanted materials were observed for 7-14 days. The vascular response of the cheek pouch membrane to tumor grafts was contrasted with that of normal human, keloid, nevocellular nevi, and inert control materials (Millipore filter and dialysis membrane). Lymphoma grafts stimulated neovascularization in the hamster cheek pouch directly and across a microporous barrier (Millipore barrier). The usual sequence of events consisted of arterial tortuosity and vasodilation, followed by early sprouting of tiny capillary buds, overgrowth of implants, and establishment of complex functioning vascular areas. Controls showed occasional tortuosity and dilation without angiogenesis. It is suggested that the diagnostically significant vascular changes often associated with human skin tumors may be due to capillary proliferation induced by a TAF. It is also suggested that cutaneous neoplasms might provide an excellent proving ground for the theory that tumor growth might be arrested by interfering with the elaboration and/or function of TAF.

4017 NUCLEAR CHARACTERISTICS OF MALIGNANT LYMPHOMA IN THE BRAIN. (Eng.) Tani, E. (Hyogo Coll. Medicine, Nishinomiya, Hyogo, Japan); Ametani, T. *Acta Neuropathol.* [*Suppl.*] *(Berl.)* 6: 167-171; 1975.

The nuclear characteristics of an intracerebral malignant lymphoma were defined by EDTA staining of formalin-fixed specimens and by enzyme extraction with RNase, DNase, or pepsin. Thin sections were examined under the electron microscope. In addition to chromatin and nucleoli, various classes of nuclear structures were often seen in the malignant lymphoma compared with other brain tumors. Interchromatin, perichromatin, and atypical granules were observed; the interchromatin granules were the most conspicuous. The perichromatin granules were found at the periphery of chromatin clumps and sometimes in the interchromatin area. The atypical dense granules also appeared occasionally in the interchromatin area. Chromatin was bleached by EDTA; the nucleoli and the perichomatin, interchromatin, and atypical dense granules were still clearly evident after staining. If pepsin and RNase were combined, the interchromatin granules appeared to decrease their electron density or could not become visible. On the basis of their reactions to enzymatic extraction and EDTA stain, the interchromatin, perichromatin, and atypical dense granules could be ribonuclearprotein in nature. Moderately dense fibrils and granules, designated perichromatin fibrils, became visible at the border of condensed chromatin bleached by EDTA. These fibrils might contain substrate for HnRNA. Nuclear bodies and intranuclear fibrillar rodlets were also evident. Although nucleoli are the main site of RNA synthesis in nuclei, these results suggest that extranucleolar synthesis occurs in malignant lymphoma.

4018 INTRAOCULAR RETICULUM-CELL SARCOMA: CLINICO-PATHOLOGIC STUDY OF FOUR CASES AND REVIEW OF THE LITERATURE. (Eng.) Barr, C. C. (Johns Hopkins Med. Inst., Baltimore, Md.); Green, W. R.; Payne, J. W.; Knox, D. L.; Jensen, A. D.; Thompson, R. L. *Surg. Ophthalmol.* 19(4):224-239; 1975.

Four patients with primary intraocular reticulum-cell sarcoma are presented. The four patients (3 women and one man) were followed at the Wilmer Institute for periods up to ten years. All had decreased visual acuity and a uveitis that was refractory to standard forms of therapy. In one case, the correct diagnosis

vas made clinically. At autopsy, two of the patients had systemic reticulum-cell sarcoma, a third had intracranial reticulum-cell sarcoma, and in a fourth case the disease process was confined to the eye. A recalcitrant uveitis was present in almost all of the cases reported. Differential diagnosis and methods of diagnosis are discussed. Patients reported here are those who had primary manifestations of reticulum-cell sarcoma in the eye, with clinical or laboratory evidence of systemic involvement either absent or appearing later. The clinico-pathologic features of the 4 cases are reviewed. Nine of these patients subsequently developed systemic involvement.

4019 DYNAMIC STUDIES OF CERTAIN LABORATORY CHARACTERISTICS IN PATIENTS WITH LYMPHOSARCOMA AND RETICULOSARCOMA. (Rus.) Vasygova, N. . (Inst. Experimental Clinical Oncology Acad. edical Science U.S.S.R., Moscow, U.S.S.R.); Manurov, A. N. *Lab. Delo* (5):292-295; 1975.

ynamic study of laboratory tests (ESR, ceruloplasmin activity, alpha$_2$-globulin, fibrinogen, and aptoglobin levels) in 14 patients with lymphosarcoma and 31 patients with reticulosarcoma (27 men, 8 women, aged 17-74 yr), as well as in 14 patients ith lymphosarcomatosis is presented. Normal ESR, eruloplasmin activity and alpha$_2$-globulin levels, ncreased fibrinogen concentration in all stages, nd decreasing haptoglobin concentration with the dvancement of the disease were observed in patients ith lymphosarcoma and reticulosarcoma. After theapy, slight increase in ESR, higher but still norl haptoglobin levels, and increased ceruloplasmin ctivity were found. The findings indicate the bsence of distinct correlations between laboratory ests and the activity and progression of the maligant process or the effectiveness of therapy in ymphosarcoma and reticulosarcoma. Increased ESR, ibrinogen, sharp increases in the haptoglobin evel and ceruloplasmin activity, and normal alpha$_2$-lobulin were found in lymphogranulomatosis.

020 FOETAL ERYTHROPOIESIS IN HUMAN LEUKAEMIA. (Eng.) Weatherall, D. J. (Nuffield Dept. linical Medicine, Univ. Oxford, Radcliffe Infirary, Oxford OX2 6HE, U.K.); Clegg, J. B.; Wood, W. .; Callender, S. T.; Sheridan, B. L.; Pritchard, . *Nature* 257(5528):710-712; 1975.

ne occurrence of fetal erythropoiesis in several orms of leukemia was studied. The subjects were ine infants or young children with juvenile chronic yeloid leukemia (JCML), 10 with erythroleukemia, 4 children and adults with acute myeloblastic leuemia, 19 with acute lymphoblastic leukemia, 30 with hronic myeloid leukemia, and 44 with chronic lymhatic leukemia. The highest levels of Hb F in ases with JCML and erythroleukemia were associated ith decreased levels of Hb A$_2$ and carbonic anhyrases B and C. Embryonic Hb was not found. Eleated levels of Hb F were observed in most of the atients with other forms of leukemia. In 15 of the 7 patients with acute myeloblastic leukemia studied, n increase in the Hb F level developed about 60 days fter the start of chemotherapy, when rapid regeneration of bone marrow was taking place. Significantly greater increases of Hb F levels were observed in those in remission. The levels of Hb A$_2$, and carbonic anhydrases B and C fell to levels found in newborns. The results indicate that in some leukemias of early childhood there may be an almost total reversion to the fetal form of erythropoiesis. They are consistent with the suggestion that childhood leukemias arise in cell lines which have escaped the normal processes of differentiation.

4021 MORPHOLOGICAL AND CERTAIN CYTOCHEMICAL CHARACTERISTICS OF ACUTE LEUKEMIAS. (Rus.) Tsyba, N. N. (A. M. Gor'kii Donetsk Medical Inst., Donetsk, U.S.S.R.); Novitskaia, V. M. *Lab. Delo* (5):279-282; 1975.

Morphological and certain cytochemical characteristics of acute leukemias were studied in 51 patients. The percentages of positive cells in the PAS reaction, myeloperoxidase, phospholipid, and acid phosphatase tests were 61.6%, 70%, 60%, and 37.8% in acute myeloblastic leukemia (15 patients). The leukocyte counts ranged from 4,000-62,000/µl, the percentage of leukemic myeloblasts was 15-96%, and the marrow myelokaryocyte count was 150,000-1,060,000/µl, with prevalence of leukemic myeloblasts (20-92%). Leukocytopenia (1,500-3,600/µl), thrombocytopenia, and a high percentage of anaplastic promyelocytes (33-61%) were found in promyelocytic leukemia (two patients). The PAS reaction was positive in 94.5%, the myeloperoxidase test in 100%, the phospholipid test in 95%, and the acid phosphatase test in 20%. The PAS reaction was positive in 61.4% of the cases, the acid phosphatase reaction in 41.13%, while the myeloperoxidase and phospholipid reactions were negative in acute lymphoblastic leukemia (19 patients). Leukocyte counts of 1,000-380,000/µl, 3-91% lymphoblasts were observed. Undifferentiated forms of acute leukemias (five patients) differed only slightly from the lymphoblastic and myeloblastic forms. Here, all reactions were negative. A special group of patients with acute leukemia was identified which was characterized by 43-90% of metaplastic leukemic marrow elements, depression of erythropoiesis and thrombocytopoiesis, 7-24% large leukemia cells, including cells with vacuolized cytoplasm, and by high acid phosphatase activity. Morphological changes without cytochemical shifts were observed in advancing, recurrent, and terminal cases.

4022 MALIGNANT MELANOMA — A PO-CELL TUMOR? (Ger.) Schmidt, H. (Physiolisch-chemisches Institut DDR-402 Halle (Saale), Hollystr. 1, East Germany); Stintz, A. R. *Arch. Geschwulstforsch.* 45(2):146-152; 1975.

Tissue samples from a primary, recurrent melanoma in a 57-yr-old patient and from a lymph node metastasis of a round-cell melanoma in a 53-yr-old patient were investigated for phenoloxidase-containing cells. Numerous scattered cells and accumulations of cells with phenoloxidase were found both in the malignant melanoma of the skin and in the lymph node metastases. In view of these findings, it is proposed that

phenoloxidase-containing cells are the stem cells of malignant melanoma, contrary to the common view that melanoma derives from the melanocytes of the stratum cylindricum of the epidermis. The occurrence of phenoloxidase-containing cells in different organs and tissues gives a good explanation for the high susceptibility of melanoma to metastases in different organs and tissues.

4023 BREAST CANCER GENETICS AND CANCER CONTROL: TUMOR ASSOCIATION. (Eng.) Lynch. H. T. (Sch. Medicine, Creighton Univ., Omaha, Nebr. 68178); Lynch, J.; Lynch, P. *Arch. Surg.* 110(10):1227-1229; 1975.

A study was made of four kindreds in which a familial association existed between carcinoma of the breast, soft tissue sarcomas, leukemia, and brain tumors. The mode of transmission was consistent with that of a Mendelian autosomal dominant genetic factor. Verified breast cancer was present in a father, his mother, and his daughter. His son has a brain tumor (by history) and his grandson, (the son of the affected daughter), had a histologically verified rhabdomyosarcoma. This familial aggregation of cancers (except for leukemia, which is absent) is consistent with a newly described familial breast cancer syndrome. A single pleiotropic, dominantly transmitted gene, possibly interacting with carcinogenic factors, such as an oncogenic virus, may be the cause. Histopathology may provide clues to familial cancer risk in certain families, and improved cancer control might be achieved through the identification of familial cancer risk for specific anatomic sites.

4024 RELATIONSHIP BETWEEN EXPERIMENTAL RESULTS IN MAMMALS AND MAN. I. CYTOGENETIC ANALYSIS OF BONE MARROW INJURY INDUCED BY A SINGLE DOSE OF CYCLOPHOSPHAMIDE. (Eng.) Goetz, P. (Res. Inst. of Child Development, Prague, Czechoslavakia); Sram, R. J.; Dohnalova, J. *Mutat. Res.* 31(4):247-254; 1975.

The extrapolation of experimental results to man was studied by cytogenetic bone marrow analysis and micronucleus test in mice, rats and Chinese hamsters. Furthermore, the frequency of chromosomal aberrations was compared with the frequencies of polychromatic RBC containing micronuclei. Cyclophosphamide (CY) was given at doses of 5, 10, 20, 40, and 80 mg/kg to ICR mice and Wistar rats; doses of 10, 20, 40, 80, 120, and 160 mg/kg were given to Chinese hamsters. Five patients with various types of malignancies until then medically untreated, were iv administered 40 mg CY/kg. Bone marrow cells were examined 24 hr after the administration. In all rodents, CY induced a clear-cut dose-effect relationship in the frequency of breaks and abnormal metaphases, as well as in the frequency of micronuclei in polychromatic RBC. When comparing the results in rodents and man at the dose of 40 mg CY/kg, the sensitivity pattern of species was mice > rats > Chinese hamsters > man. From this aspect the possible differences in the metabolism of CY in analyzed species are discussed. The results may indicate that micronucleus testing may be a very suitable method used for screening purposes; however, the method of classical cytogenetic analysis, especially the evaluation of breaks, still remains the most exact and reliable technique.

4025 HETEROCHROMATIN AND CHROMOSOME ABERRATIONS. A COMPARATIVE STUDY OF THREE MOUSE CELL LINES WITH DIFFERENT KARYOTYPE AND HETEROCHROMATIN DISTRIBUTION. (Eng.) Natarajan, A. T. (Wallenberg Lab., Lilla Frescati, S-10405 Stockholm 50, Sweden); Raposa, T. *Hereditas* 80(1):83-90; 1975.

Mitomycin C-induced chromosome aberrations in mouse cells differing in chromosome number and karyotype were studied. The cell lines included (1) laboratory mouse (2n=40), all telocentric chromosomes possessing centromeric heterochromatin, (2) laboratory mouse x tobacco mouse hybrid (2n=33) with seven metacentrics and 26 telocentrics, and (3) ascites tumor cells (MSWBS; 2n=28-29), with 9-10 biarmed chromosomes, with heterochromatin localized to the centromeric regions in all, except two marker chromosomes - one telocentric with four intercalary blocks, and one biarmed chromosome with two terminal blocks. *In vitro* cultures of fibroblasts were treated with 0.04-0.5 μg/ml mitomycin. In the case of MSWBS, the animals carrying tumors were injected with mitomycin C in isotonic saline (4 μg/ml of ascitic fluid). Both chromatid intrachanges and interchanges were scored. In laboratory mouse fibroblasts, about 80% of the aberrations were localized to the heterochromatic regions. In the tobacco mouse x laboratory mouse hybrid, the exchanges were between two telocentrics or a telocentric and a metacentric, but seldom between two metacentrics. This suggests that there must be a specific control of the association of chromocenters in the interphase and that there is a homologous association between the telocentric and metacentric. In the MSWBS tumor cells, the centromeric heterochromatin was involved more often in interchanges than the intercalary blocks, without any restriction between two biarmed chromosomes to form exchanges. A low frequency of chromatid breaks in this line may be due to the presence of an extremely efficient DNA repair system.

4026 ON THOROTRAST LEUKEMIA: EVOLUTION OF CLONE OF BONE MARROW CELLS WITH RADIATION-INDUCED CHROMOSOME ABERRATIONS. (Eng.) Visfeldt, J. (Univ. Inst. Pathological Anatomy, Juliane Maries Vej 16, DK-2100 Copenhagen Ø, Denmark); Jensen, G.; Hippe, E. *Acta Pathol. Microbiol. Scand.* [*A*] 83(4):373-378; 1975.

Chromosome studies of bone marrow cells from a 62-yr-old woman, who had been treated with Thorotrast, were undertaken. The patient had been given 40 ml of Thorotrast in connection with a neuro-radiological examination 34 yr earlier. Clinically, the patient was considered to be in an incipient myeloid leukemic phase. One hundred cells were analyzed. Ninety-seven percent of the cells belonged to a clone with characteristic marker chromosomes induced by radiation. The results of the study were compared with data from chromosome analyses of ^{32}P-treated patients with polycythemia vera, in whom large clones occurred in the bone marrow. The results of chromosome analysis of bone marrow cells from the

horotrast patient support previous hypotheses con-
erning the carcinogenesis in radiation-induced
eukemia in patients with polycythemia vera, treated
ith ^{32}P. In the latter patients, the clone cells
re presumed to represent cell populations with se-
ective qualities, originating from radiation-dam-
ged cells, which possibly possess an increased ten-
ency to malignant transformation because of a more
ronounced sensitivity to carcinogenic agents. The
ells might also be potentially malignant and mani-
est themselves as leukemia cells, if the patient's
mmunological defence mechanism is broken.

027 ON THE MUTATION RATE OF NEUROFIBROMA-
TOSIS. (Eng.) Sergeyev, A. S. (Inst.
edical Genetics, Kashirskoye shosse 6a, AMS Moscow,
SSR). *Humangenetik* 28(2):129-138; 1975.

genetic study of 124 cases of neurofibromatosis
as performed. The contingent of probands was
ainly represented by a Russian population. The
cidence of neurofibromatosis in the general popu-
tion was evaluated by examination of a population
mple of 16-yr-old youths as a model for the study.
th parents of the proband were examined in only
cases, the proportion of sporadic cases in this
oup being 0.79 as compared to 0.77 for the whole
oup under study. The existing data evaluated by
direct method are not yet sufficient for a deci-
ve estimation of the penetrance, which, however,
nnot be under 80%. Segregation analysis of de-
endants from particular marriages showed a good
rrespondence to the hypothesis of Mendelian domi-
nce (32 affected children out of 65). These re-
lts analyzed together with those obtained by other
thors permit an inference on the full penetrance
neurofibromatosis. The genetic interpretation
sporadic cases as a result of new mutations is
esented. The prevalence of neurofibromatosis
ong the 16-yr-old youths was evaluated as 12.8 x
$^{-5}$. This value is suggested to be an estimation
the incidence of the condition in the general
pulation, the mutation rate evaluated by a direct
thod being equal to $4.4 \times 10^{-5} \div 4.9 \times 10^{-5}$. The
creased birth order of probands in sporadic cases
gainst the theoretical expectation) as well as in-
eased paternal age (as compared with controls)
re found to be statistically significant (P =
004 and P = 0.03, respectively), while the differ-
ce in maternal ages was statistically insignificant
= 0.08). No statistical relationship between
oradic cases and occupational exposure of parents
deleterious chemical and physical factors was
nd. The level of clinical investigation in this
dy permits no inference on genetic heterogenicity
neurofibromatosis; thus there is no evidence to
gest that more than one locus is responsible for
disease.

8 PRIMARY TISSUE CULTURE OF HUMAN WART-DERIVED
EPIDERMAL CELLS (KERATINOCYTES). (Eng.)
mura, M. (Univ. Minnesota Med. Sch., Minneapolis);
s, F.; Wooley, R.; Soutor, C. A. *J. Natl. Cancer*
t. 54(3):563-569; 1975.

pathogenesis of wart formation was studied by maintaining epidermal cells (keratinocytes) derived from fragments of 50 warts and 16 normal skin specimens in primary tissue culture. Cultures were maintained on Dulbecco's modified Eagle's minimal essential medium with 10% fetal calf serum, L-glutamine (4.0 mM), penicillin (100 U/ml) and streptomycin (100 μg/ml) at 35 C in humidified air and 5% CO_2. Growth occurred in 37% of wart fragments as compared to 44% of normal skin. The wart keratinocytes continued to proliferate for periods exceeding three months, but their appearance and growth patterns were identical to normal skin. Electron microscopic examination of cell sheets from 20 warts and of five parent wart specimens revealed clustered virions in all nuclei of the parent warts, but no virions were detected in a minimum of 500 nuclei from each of the cultures. Precipitating antisera to purified whole human papilloma virus (HPV) virions were prepared in rabbits. Indirect immunofluorescence studies showed virions in cryostat sections of parent wart keratinizing cell nuclei, but not in wart culture nuclei. Immunoenzyme studies with horseradish peroxidase-labeled Fab fragments from anti-HPV and diaminobenzidine similarly revealed virions in parent wart but not in wart-derived cultures. Although proliferating wart-derived tissue cultures show no morphologic evidence of virus transformation or virion assembly, the cultures provide a model for further molecular studies.

4029 FAMILIAL OCCURRENCE OF WILMS'S TUMOR:
NEPHROBLASTOMA IN ONE OF MONOZYGOUS
TWINS AND IN ANOTHER SIBLING. (Eng.) Juberg, R.
C. (Louisiana State Univ. Sch. Med., Shreveport);
St. Martin, E. C.; Hundley, J. R. *Am. J. Hum.*
Genet. 27(2):155-164; 1975.

A sibship is presented in which a pathologically documented Wilm's tumor occurred in one member of a monozygous male twin pair at age two years and then, nine months later, in his 12-mo-old sibling. The twins were considered to be monozygotic because of phenotypic similarities, the probability computed from analysis of blood groups, and comparison of their dermatoglyphics. There were no other persons in the kindred with either the renal tumor or associated malformation, and the parents were not consanguineous. The tumor in each of the affected siblings appeared to be single, contrary to expectation in the hereditary form. The monozygotic unaffected twin remains without evidence of tumor at age five years. He therefore represents an exception to the hypothesis of the mutagenic origin of Wilm's tumor and provides support for an environmental etiology of nephroblastoma, at least in this family. It can be assumed that the twins were not always exposed to precisely the identical qualitative and quantitative environmental factors from conception through the first 22 mo of postnatal life.

4030 ACUTE MYELOCYTIC LEUKAEMIA AND LEU-
KAEMIA-ASSOCIATED ANTIGENS IN SISTERS.
(Eng.) Pendergrass, T. W. (Epidemiology Branch,
Natl. Cancer Inst., Bethesda, Md. 20014); Mann,
D. L.; Stoller, R. G.; Halterman, R. H.; Fraumeni,
J. F., Jr. *Lancet* 2(7932):429-431; 1975.

In a sibship of five brothers and seven sisters, three sisters died from acute myelocytic leukemia diagnosed at age 31, 37, and 42 yr, respectively. A fourth sister probably had the same disease; although her death at age 22 was attributed to Hodgkin's disease and aleukemic leukemia, her symptoms and clinical course were similar to those of the older sisters. Laboratory studies on the close relatives revealed that a fifth sister had persistently high RBC sedimentation rates (88 mm/hr) and serum immunoglobulin M levels (232 mg/100 ml). WBC from this sister were lysed by heterologous and allogeneic antisera detecting leukemia-associated antigens. This reaction has been seen previously only in patients with acute leukemia, but it may signify a preleukemic state in a normal member of a leukemia-prone family.

4031 ELEVATED PLASMA TESTOSTERONE AND GONADAL TUMORS IN TWO 46XY "SISTERS". (Eng.)
Anderson, C. T., Jr. (Univ. of Wisconsin Hosp., 1300 Univ. Ave., Madison, Wis. 53706); Carlson, I. H. *Arch. Pathol.* 99(7):360-363; 1975.

The case histories of two sisters, both of the 46XY genotype and demonstrating amenorrhea and virilization, are presented. Both patients had elevated testosterone levels in the peripheral venous blood (250 ng/dl in patient 1). Laparotomy was performed in both sisters who, within a period of two months, were shown to have identical conditions. At laparotomy patient 1 had a 644-g, 17 x 8 x 10-cm, firm nodular mass removed from the left adnexa. Tumor venous effluent showed an elevated testosterone level (6,100 ng/dl). Microscopic examination revealed a dysgerminoma in the right and left ovarian regions, probably arising from a preexisting gonadoblastoma (this was evidenced by the presence of areas of laminar calcification on the tumor). Patient 2, at laparotomy, showed an infantile uterus. Microscopically, the ovaries showed a dysgerminoma and a gonadoblastoma on the left side and a pure gonadoblastoma on the right side. The tumors of both patients had nests of Leydig-like cells and may be the source of the androgen. The author postulates that these sisters were chromosomal males (possibly XO/XY mosaic) who developed internal and external female genitalia. The gonadoblastoma is then thought to have developed in dysgenetic gonads that were the androgen source. Further, some peripheral ovarian stroma may have provided the estrogen, which resulted in breast formation. As the tumor grew and altered to a dysgerminoma, the surrounding stroma may have become compressed, reducing estrogen and increasing androgen production.

4032 FAMILIAL HAEMOPHAGOCYTIC RETICULOSIS. REPORT OF 2 CASES IN SIBS. (Eng.) Botha, J. B. C. (Dept. Pathology, Univ. Cape Town, South Africa); Kahn, L. B.; Kasrhula, R. O. C. *S. Afr. Med. J.* 49(32):1305-1308; 1975.

A four yr old girl and her five mo old brother showed familial hemophagocytic reticulosis. The disease is characterized by a widespread proliferation of histiocytes showing hemophagocytosis and it usually manifests clinically with hematological abnormalities. The initial presentation may be that of a meningo-encephalitic illness, the result of a lymphohistiocytic infiltration of the meninges and cerebral tissues. Steroid therapy given to the girl before hospitalization had helped in some clinical improvement of neurological deficit but her condition deteriorated and she developed fever, hepatosplenomegaly, with jaundice and abnormal liver function. Before her death, hemolysis, granulocytopenia and thrombocytopenia were noted. The boy's illness had many features in common with disease process. The significance of abnormalities of his serum lipid pattern is not yet clear.

4033 HEMOPHAGOCYTIC RETICULOSIS: A CASE REPORT WITH INVESTIGATIONS OF IMMUNE AND WHITE CELL FUNCTION. (Eng.) Fullerton, P. (Royal Children's Hosp., Melbourne, Victoria 3052, Australia); Ekert*, H.; Hosking, C.; Tauro, G. P. *Cancer* 36(2):441-445; 1975.

A five-month-old boy with hemophagocytic reticulosis is described. The diagnosis was made on the basis of hepatomegaly, pancytopenia, and the presence in bone marrow aspirates of many primitive neoplastic histiocytes, some of which were actively phagocytosing RBC. Immunologic investigations revealed a grossly defective phytohemagglutinin (PHA) response of the patient's lymphocytes which improved with chemotherapy (6 mg/m^2 vinblastin and 100 mg/m^2 prednisolone). Low immunoglobulin A levels (16-20 IU/ml) and defective glucose oxidation by phagocytosing cells were demonstrated at diagnosis and have persisted despite chemotherapy. The lack of a normal increase in glucose oxidation after phagocytosis, combined with a normal or greater than normal resting glucose oxidation, suggested that WBC were unable to stimulate the hexose monophosphate shunt following phagocytosis. HL-A typing and chromosome studies did not reveal maternal lymphocytes in the child's circulation; thus, a graft *vs* host reaction caused by maternofetal transplant of histiocytes was apparently not involved in the pathogenesis of hemophagocytic reticulosis in this patient. The improvement in PHA response which occurred despite treatment with immunosuppressive drugs suggests that immunodepression may be part of the pathogenesis of this disorder. The persistence of the defect in phagocytosing glucose oxidation despite treatment indicates that this may also be related to the pathogenesis of the disease. The patient remains well after 11 mo of treatment with vinblastine and prednisolone.

4034 ENDOCRINE-TYPE GRANULES IN CELLS OF GLOMUS TUMOR OF THE STOMACH. (Eng.)
Kim, B. H. (Lutheran Medical Center, Brooklyn, N.Y. 11220); Rosen, Y.; Suen, K. C. *Arch. Pathol.* 99(10): 544-547; 1975.

The ultrastructure of a glomus tumor removed from the pyloric region of the stomach of a 57-yr-old

woman was studied. The tumor possessed structural features similar to those of smooth muscle cells, i.e., it contained pinocytic vesicles and numerous filaments with focal condensation. In addition, previously undescribed endocrine-type granules and cilia were identified. The endocrine-type granules were diffusely present in the cytoplasm but were often seen in greater concentrations adjacent to the Golgi complex. The majority of granules were of uniform density and were surrounded by a single membranous structure. Some of the granules were in close contact with the protoplasmic membrane, but no granules were seen outside the membrane. The cilia were found in only a few tumor cells; these were of a rudimentary nature and protruded into the intercellular spaces. The presence of the endocrine-type granules suggests that gastric glomus tumor cells possess not only contractile properties, but also secretory activity.

4035 METASTATIC GROWTH OF HUMAN TUMOUR XENOGRAFTS IN THYMECTOMISED IRRADIATED MICE RECONSTITUTED WITH SYNGENEIC BONE MARROW CELLS. (Eng.) Franks, C. R. (Guy's Hosp., London, SE1 9RT England); Boulger, L. R.; Garrett, A. J.; Bishop, D.; Reeson, D.; Perkins, F. T. *Eur. J. Cancer* 11(9):619-622; 1975.

The metastatic growth of human tumors in thymectomized, irradiated CBA mice was studied. In 160 mice implanted sc with HeLa tumor specimens, 13 cases of metastatic growth were found. Tumor specimens from 51 patients were implanted into 302 mice. Metastases were found at autopsy in mice into which 2 melanomas, a colon, a rectal, and a squamous cell carcinoma had been implanted. Nine out of the total 18 cases were to lymph nodes; 8 out 18 to lung, and 1 out 18 to spleen. In contrast to these findings, metastases from HeLa tumors do not occur in mice treated with antilymphocyte serum.

4036 ALTERATIONS OF LIVER AND SPLEEN AMONG WORKERS EXPOSED TO VINYL CHLORIDE. (Eng.) Popper, H. (Mt. Sinai Sch. Med., City Univ. New York, N.Y.); Thomas, L. B. *Ann. N.Y. Acad. Sci.* 246:172-194; 1975.

A preliminary review of hepatic biopsy and autopsy specimens obtained from 11 patients exposed to vinyl chloride (VC) in the polymerization of polyvinyl chloride (PVC) is presented. The incidence of each lesion was recorded, and hematoxylin and eosin stains, connective tissue stains, and silver impregnations were employed. Liver without angiosarcoma showed fibrosis in which the portal tracts were enlarged to varying degrees; a moderately dense lymphocytic infiltration intermixed with some histiocytes was noted, and the lobular architecture was entirely preserved. Throughout most livers, there was a proliferation of sinusoidal lining cells, some of which were macrophages with PAS-positive granules. There were also enlarged hepatocytes, consisting of increased cytoplasm and large and hyperchromic nuclei. Focal, chiefly centrolobular, canalicular cholestasis were also seen which was accentuated in the centrolobular zone. In the hepatic parenchyma of patients afflicted with angiosarcoma of the liver, the same general alterations were found; of particular interest was the frequency of the focal conspicuous dilatation of sinusoids not related to lobular topography. Splenic alterations, with or without hepatic angiosarcoma, included enlarged organs with grossly visible and conspicuously enlarged organs with grossly visible and conspicuously enlarged Malpighian follicles. The focal subcapsular fibrosis was the single most conspicuous lesion in the precursor stage, while neither the portal fibrosis nor intralobular fibrosis was considered pathognomic. The study suggests that the angiosarcoma results from the stimulation of various hepatic and splenic cells by VC or its metabolites, presumably formed in the liver. The cause of activation of the hepatocytes may be either a primary stimulation by VC or a response to a hepatocellular injury caused by the reagent.

4037 MALIGNANT PERITONEAL MESOTHELIOMA AFTER CHOLANGIOGRAPHY WITH THOROTRAST. (Eng.) Maurer, R. (Pathologisches Institut, Kantonsspital, Brauerstrasse 15, CH-8401 Winterthur, Switzerland); Egloff, B. *Cancer* 36(4):1381-1385; 1975.

A report is made of a malignant peritoneal mesothelioma occurring 36 yr after thorotrast administration. A female patient had undergone cholecystectomy after displaying symptoms of gallbladder disease; during a cholangiogram performed with thorotrast at operation, the contrast medium spilled around the bile duct. Twenty-five years later, hypertension and a nonfunctioning right kidney led to nephrectomy. Histologically, there was no functioning renal tissue or normal transitional epithelium. Large amounts of thorium dioxide identified microscopically and by autoradiography led to a diagnosis of hydronephrosis due to thorotrast-induced fibrous stenosis of the pyeloureteral junction. After 36 yr, upper abdominal pains occurred. Abdominal roentgenograms still showed deposits of contrast medium in the right upper abdominal quadrant, and death followed the development of ascites, recurrent paralytic ileus, and anuria. At autopsy, the serosa of the small intestine was found to be entirely covered by tumor. Microscopically, the tumor consisted mainly of solid sheets of irregular round cells with hyperchromatic nuclei and various amounts of ill-defined cytoplasm. The tumor showed varying sarcomatous and carcinomatous patterns. While paravertebral lymph nodes contained thorium dioxide and tumor tissue, there was no evidence of distant metastases. The tumor is thus considered to represent a case of radiation-induced peritoneal mesothelioma.

4038 MOUSE MAMMARY TUMORS: ALTERATION OF INCIDENCE AS APPARENT FUNCTION OF STRESS. (Eng.) Riley, V. (Dept. of Microbiology, Pacific Northwest Res. Foundation, Seattle, Wash. 98104). *Science* 189(4201):465-467; 1975.

The effect of different experimental and environ-

mental conditions on mammary tumor incidence and latency was studied in C3H/He mice carrying the Bittner strain of mammary tumor virus. From 80-100% of these mice usually develop mammary tumors within 8-18 mo after birth when studied under the usual housing and experimental conditions. Four groups of mice were investigated: parous mice housed under conditions of chronic environmental and manipulative stress (group A); nonparous mice housed under the same conditions of chronic environmental and manipulative stress (group B); nonparous mice housed under protective conditions and subjected to moderate intermittent stress (group C); and mice provided with maximum protection from environmental and manipulative stress (group D). The last group was a combination of parous, nonparous, and virgin mice delivered by cesarean section and foster-nursed to deplete the milk-passaged tumor virus. The median tumor latency period for group A was 276 days compared with 358 days for group B. In group C the median latency period was 566 days, a significant extension over both groups A and B. At 400 days of age, the incidence of spontaneous mammary tumors was 92% in group A, 60% in group B, and 7% in group C. Group D had such a small tumor incidence that determination of a median latency period was not possible. At 21 mo of age, only one mammary tumor was detected in 75 surviving mice. The data suggest that moderate chronic or intermittent stress may predispose C3H/He mice to an increased risk of mammary carcinoma, possibly through a resultant compromise of their immunological competence or tumor surveillance system, and that adequate protection from physiological stress may reduce the occurrence of the mammary tumors.

4039 PARTICIPATION OF MYCOPLASMAS IN ONCOGENESIS. (Ger.) Gerlach, F. (Kubeckgasse 12, A-1030 Wien, Austria). *Wien. Med. Wochenschr.* [*Suppl.*] 26 (4):1-12; 1975.

The carcinogenicity of cell-free Mycoplasma preparations isolated from malignant human and animal tumors (carcinomas, sarcomas, hypernephromas, leukemias, lymphogranulomatoses), as well as from normal fetuses, umbilical cords, and placentae was studied in pathogen-free NMRI mice. To achieve long-term exposure, sc depot inoculation was used. Malignant tumors developed in 190 of the 209 inoculated animals (90.9%), while the tumor incidence among 600 control animals was 0.83%. The type of the tumor was independent of the type of the tumor from which the Mycoplasma preparation was obtained. The incidence of multiple tumors was 30.5%. Manifest tumor was preceded by preblastomatous processes, such as polyserositis, hyperplasia of the lymph nodes and of the spleen, and by adenomatous proliferations in inner organs. It is concluded that Mycoplasmas are ubiquitous infective agents specific for tumor induction in general, but not for any particular morphological type or localization. No malignant tumor occurs without the presence of Mycoplasmas, while numerous Mycoplasma infections do not provoke malignant tumors.

4040 COMMON AND UNCOMMON MELANOCYTIC NEVI AND BORDERLINE MELANOMAS. (Eng.) Reed, R. J. (Dermatopathology Lab., 1430 Tulane Ave., New Orleans, La. 70112); Ichinose, H.; Clark, W. H., Jr.; Mihm, M. C., Jr. *Semin. Oncol.* 2(2):119-147; 1975.

The histologic parameters that distinguish less common, benign melanocytic tumors from common acquired melanocytic nevus are described, and the biologic significance of the deviant patterns is discussed. The histologic diagnosis of evolving malignant melanoma is also reviewed with emphasis on growth phases that are correlated with a good prognosis. Benign tumors discussed include acquired blue nevus, congenital nevus, Spitz tumor, and pigmented spindle cell nevus, as well as acquired melanocytic nevus. Nevus cell patterns in these tumors are compared with those in cytologically borderline lesions including malignant melanomas, halo nevi, and minimal deviation melanomas arising in congenital nevi, spindle cell melanomas, and malignant blue nevus (minimal deviation patterns). Cytologically malignant, biologically indolent melanomas (radial growth phase melanomas) are assessed on the basis of the level of invasion, and it is noted that lesions that have not invaded the dermis or that lack the capacity to survive and actively proliferate in the dermis are biologically borderline lesions with good prognoses. The significance of the host's immune response in regressing melanomas, especially superfical spreading melanomas, is briefly discussed. A brief discussion is also included of two unusual histologic patterns in melanocytic tumors that may be confused with those of evolving melanomas; these are the sheath cell reaction and recurrent nevi.

4041 MULTIFOCAL COLONIC CARCINOMA AND CROHN'S DISEASE. (Eng.) Keighley, M. R. B. (Queen Elizabeth Hosp., Edgbaston, Birmingham, England); Thompson, H.; Alexander-Williams, J. *Surgery* 78(4):534-537; 1975.

A case report of a 65-yr-old man with a 13-yr history of Crohn's disease and multifocal colonic carcinoma is presented and the relation between the two is discussed along with a review of the literature. A barium enema revealed a large polypoid mass in the transverse colon. Also noted were loss of haustral markings and irregular mucosal outline in the proximal colon, and a small polyp in the sigmoid colon. Biopsy was consistent with Crohn's disease. At laparotomy Crohn's disease was found to involve the distal ileum and the entire colon. In addition to the polyps detected by barium enema, two more were found in the ascending colon, one in the transverse and one in the sigmoid. All six polyps were well-differentiated papillary adenocarcinomas of the mucosa only. A lesion in the cecum was also found to be a well-differentiated adenocarcinoma of the mucosa only. Other recent reports and reviews have shown a higher incidence of carcinoma of the bowel in patients with Crohn's disease. A review of reported patients included 34 people with Crohn's disease, four of whom had multiple carcinomas of the bowel; the remainder had only single carcinomas. This incidence of multiple lesions is higher than the incidence of multiple lesions without preexisting inflammatory bowel disease. It is suggested that multiple carcinomas of the bowel are more frequent, and that colonic carcinomas are more common, in patients

with Crohn's disease than would be expected in the normal population.

4042 MUCOEPIDERMOID CARCINOMA ARISING WITHIN A WARTHIN'S TUMOR. (Eng.) Gadient, S. E. (Gundersen Clinic, Ltd., 1836 South Ave., La Crosse, Wis. 54601); Kalfayan, B. *Oral Surg.* 40(3):391-398; 1975.

A case of low-grade mucoepidermoid carcinoma arising within a Warthin's tumor is reported. The carcinoma appeared to have originated from the hyperplastic atypical epithelium of the Warthin's tumor. The histologic pattern of the carcinoma consisted of sheets of squamous, intermediate, and mucus-secreting cells occasionally lining glandular or cystic spaces. Part of the hyperplastic epithelium of the Warthin's tumor appeared squamous in type, but intercellular bridges were scarce and keratinization was lacking. Elsewhere, the hyperplastic epithelium showed mild dysplasia. The mucoepidermoid carcinoma did not infiltrate the capsule of the lymph node in which the Warthin's tumor developed. After six yr of follow-up, there is no evidence of recurrence or metastasis. The presence of metaplastic epithelium was mentioned in three previously reported cases of carcinoma complicating Warthin's tumor. The hyperplasia and dysplasia noted in the metaplastic epithelium in the present case suggest that disturbances in epithelial growth may precede the development of carcinoma in a benign Warthin's tumor.

4043 THYMOMA ASSOCIATED WITH PURE RED CELL APLASIA, IMMUNOGLOBULIN DEFICIENCY AND AN INHIBITOR OF ANTIGEN-INDUCED LYMPHOCYTE TRANSFORMATION. (Eng.) Geary, C. G. (Manchester R. Infirm., England); Byron, P. R.; Taylor, G.; MacIver, J. E.; Zervas, J. *Br. J. Haematol.* 29(3):479-485; 1975.

A case of thymoma associated with pure red cell aplasia and hypogammaglobulinemia in a 56-yr-old man is described. The aplasia occurred abruptly following removal of the tumor. Sensitivity to 2,4-dinitrochlorobenzene was not evident, suggesting that ability to produce a primary cell-mediated immune response was depressed or absent. Phytohemagglutinin (PHA) and tuberculin PPD were each cultured at concentrations of 250, 400, and 500 U/ml with 10^6 of the patient's lymphocytes in 20% autologous normal human serum or with serum taken either before or after 6-mercaptopurine (6-MP) treatment. The blastogenic response was assayed by scintillation counting after three hours of exposure to tritiated thymidine. The response was normal to PHA but, in spite of a positive tuberculin skin test, no blastogenic response was seen at any PPD concentration with lymphocytes suspended in pre-6-MP-treatment serum. A normal response was seen when culturing took place in 6-MP-treated serum and normal serum. At the same time, erythroblasts reappeared in the marrow when the patient was treated with 6-MP. This demonstrates the presence of a serum inhibitor of antigen-induced lymphocyte transformation, present previous to 6-MP administration, which was removed or reduced after immunosuppression therapy. It is suggested that the triad of thymoma, pure red cell aplasia and immunoglobulin deficiency are manifestations of the interference of an antibody to a common stem-cell component; in this case the inhibition of lymphocyte transformation may have been related to the factor which also inhibited red cell maturation.

4044 METASTATIC THYMOMA WITH MYASTHENIA GRAVIS AND PURE RED CELL APLASIA. (Eng.) DeSevilla, E. (Washington Univ. Sch. Medicine, 510 S. Kingshighway, St. Louis, Mo. 63110); Forrest, J. V.; Zivnuska, F. R.; Sagel, S. S. *Cancer* 36(3): 1154-1157, 1975.

A 64-yr-old man with a nine-year history of myasthenia gravis presented with left hip pain. Radiography of the pelvis revealed a poorly defined lytic area in the inferior left iliac wing; biopsy showed this to be a metastatic thymoma. A large anterior mediastinal mass was apparent in chest films. Over a two-week period, the left ilium received 3,000 rads through anterior and posterior portals using ^{60}Co. The mediastinal mass was treated with 3,680 rads anteriorly and 1,040 rads posteriorly, also with ^{60}Co. The anterior mediastinal mass slowly decreased in size and the patient remained well except for cholecystitis with cholelithiasis, which necessitated cholecystectomy four months later. Despite the good response to radiotherapy, the patient was readmitted the following year with severe anemia (Hb 6 g; WBC 6,500/mm^3) and pure red cell aplasia. A bone marrow aspirate showed normal megakaryocytic and granulocytic precursors, but no erythrocytic precursors. A film of the pelvis now indicated a lytic area in the right ileum, which was irradiated with ^{60}Co. The red cell aplasia remains unresponsive to anabolic steroids or cyclophosphamide. The pathophysiologic relation of myasthenia gravis and pure red cell aplasia with thymomas is not clear, although an autoimmune disorder is frequently postulated.

4045 DO GENERALIZED METASTASES OCCUR DIRECTLY FROM THE PRIMARY? (Eng.) Bross, I. D. J. (Roswell Park Mem. Inst., Buffalo, N.Y.); Viadana, E.; Pickren, J. *J. Chronic Dis.* 28(3):149-159; 1975.

Based on 4,728 autopsy reports obtained between 1965-1970, a survey of primary and metastatic cancer sites was made. The data were statistically analyzed to determine whether or not dissemination of metastases from a given primary site is basically a one-step or a multi-step process. Average numbers of metastases were arranged in tables showing the metastases' primary sites and indicating whether or not they had metastasized in certain key sites (lung and liver). In the absence of both lung and liver metastases, the generalized form of cancer was rare (the total number of metastases usually averaged less than three). Whenever metastases were reported in both liver and lung, the generalized form was usually seen at autopsy. This indicates a multistep metastatic process in which the primary cancer seeds a specific intermediate site from which the

cancer is further disseminated. When neither of the key sites were reported, the average number of metastases showed marked differences from one primary to another, suggesting initial differences between primary sites in their metastatic ability. When both key sites are positive, the average number of metastases is similar. The distinctions between primary sites thus diminish once generalization occurs and the generalized disease can be considered as a separate entity.

4046 THE RELATIONSHIP OF HISTOLOGY TO THE SPREAD OF CANCER. (Eng.) Viadana, E. (Dept. Biostatistics, Roswell Park Memorial Inst., Buffalo, N.Y. 14263); Bross, I. D. J.; Pickren, J. W. *J. Surg. Oncol.* 7(3):177-186; 1975.

Autopsy records of 4,728 patients were studied to determine the relationship between tumor histology and the metastatic spread of cancer. The various metastatic sites were grouped into four categories: the endocrine system, the lymphatic system, the CNS, and a "remainder" category, which included parenchymatous organs and the lymphatic system. The number of metastases within each system was analyzed by chi-square analysis for males (581) and females (540). Adenocarcinomas and oat-cell carcinomas of the lungs were more aggressive in their metastatic spread than were squamous cell carcinomas in the lung. Similarly, adenocarcinomas of the uterine cervix tended to metastasize more than cervical squamous cell carcinomas. There were no differences in the metastatic spread of transitional cell carcinomas and adenocarcinomas in the bladder and kidney; the results were similar for men and women. Cystadenocarcinomas of the ovaries appeared to be less widespread than adenocarcinomas of the same site. The results suggest that adenocarcinomas in general may be more aggressive in metastatic spread than other histological types.

4047 HISTOGENESIS OF LEIOMYOMATOSIS PERITONEALIS DISSEMINATA (DISSEMINATED FIBROSING DECIDUOSIS). (Eng.) Parmley, T. H. (Johns Hopkins Hosp., Baltimore, Md. 21205); Woodruff, J. D.; Winn, K.; Johnson, J. W. C.; Douglas, P. H. *Obstet. Gynecol.* 46(5):511-516; 1975.

The clinical course and histopathology in two cases (both 36-yr-old Negro women) of leiomyomatosis peritonealis disseminata were studied, and their case reports are presented. Decidual reactions in the endocervix, the uterine tube, the pelvic lymph nodes, and in multiple subperitoneal sites in the abdominal cavity were seen, and the gradual replacement of the decidua by fibroblastic proliferation was noted. In addition to routine hematoxylin and eosin staining; trichrome, reticulum, and PAS stains were used to define the cellular elements. In the two cases (one seen immediately after delivery and the other six years after delivery of normal children) the long fibrillar cells resembled fibroblasts. The nodule contained dilated capillaries with an associated inflammatory reaction and the predominant architecture suggested a stromal or fibrocytic proliferation. The special stains demonstrated a single cell rather than a "bundle" cell arrangement. Within the nodules and peripherally, foci of decidual cells remained. It is suggested that the stimulus that initiates the replacement of decidua by fibrous tissue is similar to that seen at other sites of repair and replacement. The fact that this process occurs in pregnancy suggests that it is the result of continuous stimulation of the decidua by progesterone and estrogen. Although the presence of mitotic figures in what appears to be smooth muscle scattered throughout the peritoneal cavity suggests the diagnosis of malignancy, leiomyomatosis peritonealis disseminata is believed by the authors to be the result of a benign fibrous replacement of decidual tissue. This condition may be identified by the following histologic features: (a) cells are quite long and fibrillar and more closely resemble fibroblasts than muscle cells; (b) their arrangement is more that of stroma than of the bundles of true muscle tissue; and (c) there is a dilated capillary vasculature and an associated inflammatory reaction. The presence of decidual cells within or at the periphery of the nodule together with a recent pregnancy confirms the diagnosis.

4048 OSTEOGENIC SARCOMA ASSOCIATED WITH INTERNAL FRACTURE FIXATION IN TWO DOGS. (Eng.) Banks, W. C. (Dept. Veterinary Medicine and Surgery, Texas A&M Univ., College Station, Tex. 77843); Morris, E.; Herron, M. R.; Green, R. W. *J. Am. Vet. Med. Assoc.* 167(2):166-167; 1975.

4049 MALIGNANT TRANSFORMATION OF BENIGN OSTEOBLASTOMA. A CASE REPORT. (Eng.) Seki, T. (Sch. Med., Keio Univ., Tokyo, Japan); Fukuda, H.; Ishii, Y.; Hanaoka, H.; Yatabe, S.; Takano, M.; Koide, O. *J. Bone Joint Surg.* [*Am.*] 57A(3):424-426; 1975.

4050 GIANT INTRA-ARTICULAR OSTEOCHONDROMA OF THE KNEE: A CASE REPORT. (Eng.) Sarmiento, A. (Univ. Miami Sch. Medicine, Miami, Fla.); Elkins, R. W. *J. Bone Joint Surg.* [*Am.*] 57A(4):560-561; 1975.

4051 SARCOMA IN THE REGION OF ENCEPHALITIC ALTERATIONS [abstract]. (Ger.) Boellaard, J. W. (Tubingen, West Germany). *Zentralbl. Allg. Pathol.* 119(3):228; 1975.

4052 ULTRASTRUCTURE OF A TUMOR OF THE TERMINAL PLATE [abstract]. (Ger.) Weindl, A. (Munchen, West Germany); Fahlbusch, R.; Stochdorph, O. *Zentralbl. Allg. Pathol.* 119(3):227; 1975.

4053 EXTERNAL TEMPORAL BIOPSY IN A CASE OF INFILTRATING LIMBIC GLIOMA: STUDY OF ASTROCYTIC MEMBRANOUS WRAPPING WHORLS. (Fre.) Mikol, J. (Faculte de Medicine Cochin-Port Royal, Centre Psychiatrique Sainte Anne, I Rue Cabanis, F-75674 Paris Cedex 14, France); Brion*, S.; Thurel, C. *Acta Neuropathol. (Berl.)* 32(4):347-352; 1975.

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See also:

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4113 ENVIRONMENTAL FACTORS IN CANCER INDUCTION: APPRAISAL OF EPIDEMIOLOGIC EVIDENCE -- LEUKEMIA, LYMPHOMA, AND RADIATION. (Eng.) Jablon, S. (Natl. Res. Council, Washington, D. C.). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 239-243.

The hypothesis that human leukemogenesis follows a dose-response function which is linear in the neutron dose and quadratic in the gamma-ray dose was considered on the basis of data on leukemia mortality among the Japanese A-bomb survivors. Because of the differences in the construction of the Hiroshima and Nagasaki bombs, the Hiroshima weapon emitted large quantities of fast neutrons. For most survivors in Hiroshima, the estimated kerma (kinetic energy released in materials) from neutrons was about 1/4 that from gamma rays. The Nagasaki weapon emitted few neutrons and the Nagasaki survivors received gamma radiation with a very small admixture of neutrons. About 65% of leukemias which occurred in the survivors have been acute leukemias and 35% chronic myeloid; there were no cases of chronic lymphatic leukemia. Leukemias began to occur in the Japanese survivors about 2 yr after the bombings and reached a peak in 1950-1954. The standardized mortality ratio was more than 50 among survivors whose doses were more than 100 rads. In 1970-1972, the ratio was 5.6. The leukemia mortality data for the two cities was fitted, using weighted least squares, to formulas for the probability of death from leukemia in the period 1950-1972; in one formula the neutron and gamma doses each entered as first degree terms; in the second formula the neutron dose entered as a first degree term, while the gamma-ray dose entered only as a square. For the equation linear in both neutrons and gamma rays, there was one discrepancy of large magnitude; among Nagasaki survivors who received more than 200 rads, the formula predicts 6.5 deaths, whereas 15 actually occurred. For the second equation, agreement was satisfactory in every one of the dose cells, including the Nagasaki high-dose cell. Previously published data on the induction of mammary neoplasms in rats, on opacification of the murine lens, and on a number of effects arising from irradiation of dry corn seeds coupled with the data from this investigation leads to the suggestion that a derangement of DNA is the mechanism common to these varied systems. Production of double-stranded DNA breaks should be a two-hit phenomenon for low linear energy transfer (LET), but should appear to be a one-hit phenomenon for high LET radiations such as neutrons. This evidence points to the double-stranded DNA break as being the radiation-produced lesion responsible for radiogenic leukemia.

4114 A COHORT ANALYSIS OF U.K. CANCER INCIDENCE TRENDS FOR CERTAIN SITES. (Eng.) Waterhouse, J. A. H. (Birmingham Regional Cancer Registry, Birmingham, England). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 180-190.

Evidence for 1960-1971 trends in morbidity rates of cancer of certain anatomical sites was assessed on basis of statistics accumulated at the Cancer Registries of Birmingham in the British midlands and of the southeastern part of England including half of the London area. Mean annual incidence rates by site, sex and age for three time periods in a span of 12 yr were computed and the points plotted to form a cohort incidence line. In their composite pattern, the cohort incidence lines closely approximated the contour incidence curves which represented the morbidity risk by age for a given time period. Similar to the trend world-wide, the rate of incidence of stomach cancer declined in younger age groups. The rate of incidence of cancer of the breast in females and ovarian cancer increased in younger populations, whereas in older females the rate of endometrial cancer has increased. Rates for cancer of the bladder, pancreas, larynx and bronchus all showed definite increases. Among males, the rate of increase of lung and laryngeal cancer has diminished to zero, however in females it has been increasing sharply. Evidence incriminating cigarette smoking in lung and laryngeal cancer is very strong. Morbidity data from cancer registries may provide information of predictive value.

4115 ASSESSING TRENDS OF CANCER INCIDENCE IN SMALL POPULATIONS. (Eng.) Steinitz, R. (Israel Cancer Registry, Jerusalem, Israel); Costin, C.; Katz, L. *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 175-179.

Morbidity data from the time periods 1960-1964 and 1965-1969 are used to compute the range of change in cancer incidence in the population of Israel. Several aspects of the population create a unique situation for epidemiological research: (1) total population is small, less than three million; (2) official census statistics divide the population into Jews and non-Jews; (3) the population can be analyzed on the basis of continent of origin as well as country of origin; (4) the age structure of the Israeli population is bizarre because of the arrival of immigrants in successive waves. The population at risk in each of the two time periods was calculated as the sum of the average population in each year. It was decided to use the World population rather than the total Jewish population as the population at risk and age-specific incidence rates were adjusted to this figure. Data was tabulated rather than graphed because of the small numbers involved. Reliability of the results from the two time periods was checked by investigating the incidence of cancer in two sites with anticipated opposite trends, i.e. cancer of the stomach and lung cancer. Overall reliability and comparability of the cancer registry data was also checked by analyzing the incidence rate of all malignancies. Significance tests cannot be applied to cancer morbidity data from Israel at the present time, however trends are revealed which warrant further investigation.

4116 THE CHANGING PATTERN OF CANCER IN SOUTHERN AFRICA. (Eng.) Keen, P. (Cancer Res. Unit, South African Inst. for Medical Res., Johannesburg, South Africa). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 215-221.

Trends in the incidence of lung, esophageal and liver cancer in the South African Negro are discussed with data from hospitals in Johannesburg and the Eastern Transvaal. Lung cancer which represented 8% of cancers in Bantus at the Johannesburg Hospital in 1950 increased to 52% in 1968. African Negroes in urban areas are taking up smoking cigarettes, and air pollution in native urban areas is high. The high incidence of antral cancer, 13%, can be traced to the use of a snuff containing large amounts of aromatic hydrocarbons, chromium, and nickel. Incidence of primary liver cancer appears to have peaked around 1955 and, for unknown reasons, is rapidly declining. Esophageal cancer, extremely rare before 1950, has become the commonest malignancy in some areas of South Africa. The cancer first appeared in southernmost areas, and each year the number of cases diagnosed in the indigenous population increases in an apparent chronological order from South to North. No explanation for the reversal of the incidence of lung and esophageal cancers is given.

4117 MULTIPLE PRIMARY MALIGNANCIES: INDEX TUMORS OF THE BREAST AND REPRODUCTIVE ORGANS. (Eng.) Schoenberg, B. S. (Mayo Graduate Sch. Medicine, Rochester, Minn.); Christine, B. W. *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 294-299.

The occurrence of multiple primary malignancies for which at least one of the tumors was within the breast or reproductive organs was investigated using the Connecticut Tumor Registry (1935-1964) as a data base. The study followed a group of 18,010 women and 130 men with breast cancer, and a group of 17,405 women and 8,228 men with cancer of the genital organs for the development of subsequent primary cancer of any site. In addition, 121,460 patients with a first primary malignancy of any site were followed for the subsequent occurrence of primary malignant tumors of the breast and reproductive organs. The overall survival experience for patients with a first primary malignancy was converted to person-years of exposure. The survival experience for all patients with a first primary cancer of either the breast or reproductive organs was accumulated. Age-, sex-, and site-specific incidence rates were applied to the appropriate person-years of exposure to obtain the expected number of primary cancers for each group. The coded records of reported cases were selected and matched with the first primary cancers to obtain the observed number of second primaries. Using the same methods, it was possible to determine the expected number of primary neoplasms of the breast and genital organs following primary malignancies of other sites. Excesses of observed-to-expected second primary cancers occurring in paired organs, in organs with the same system, or in structurally or functionally related organs might be explained on the basis of related tissue being exposed to the same oncogenic factors. Excesses occurring in organs apparently unrelated functionally or anatomically, in which the association goes only one way may be caused by something unique about patients with cancer at site 1 that predisposes them to develop cancer at site 2, such as a treatment regimen. For those cases with a two-way association, it may be that the same genetic or environmental oncogenic factors operating in the development of the first cancer were again operating in the development of the second cancer.

4118 CANCER MORTALITY AMONG MORMONS. (Eng.) Enstrom, J. E. (Sch. Public Health, Univ. California, Los Angeles, Calif. 90024). *Cancer* 36(3):825-841; 1975.

A study was conducted on cancer mortality among Mormons (a religious group in which the use of tobacco, alcohol, coffee, and tea is forbidden, and the use of wholesome grains and fruits and moderation in meat consumption are recommended). Data were taken from state mortality figures, from church records, and from a 1965 Alameda County, California study of health and lifestyles. Preliminary results show that the 1970-1972 cancer mortality rate among California Mormon adults is about one-half to three-fourths that of the general California population for most cancer sites, including many sites with an unclear etiology. Initial indications are that Mormons as a whole smoke and drink about half as much as the general population, and that active Mormons abstain almost completely from tobacco and alcohol. They appear to be similar to the general white population in other respects such as socioeconomic status and urbanization. The average age-adjusted total mortality ratio for nonsmokers at least 35 yr old to United States whie men in 1960 was 55%, with a range from 46-64% in the eight studies from which these figures were taken. The 1970-1972 age-adjusted total mortality ratio for California Mormon men at least 35 yr old was 46-69%, depending on the age distribution assumed. These mortality rates may considerably overestimate the mortality rates for observant lifetime Mormons, because a large proportion of Mormons have followed or still follow a lifestyle similar to the general population; 40% of Mormons in California are converts, having entered the church as adults, and another 40% are inactive and tend to ignore Mormon health practices. Low cancer rates as those seen in the Mormons have not been observed in any other group of Americans except Seventh-day Adventists. These low rates suggest the development and exploration of new etiologic hypotheses for cancer and may lead to understanding a lifestyle that produces low risk to cancer of all types.

4119 EPIDEMIOLOGIC SIMILARITIES AND DIFFERENCES IN CHILDHOOD LEUKEMIA. (Eng.) Vianna, N. J. (New York State Dept. Health, 84 Holland Ave., Albany, N. Y. 12208); Polan, A. K.

Proc. Int. Cancer Congr. 11th. Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 276-281.

Epidemiological data on cases of leukemia, nine years of age or less, occurring in New York State in the period 1950-1970 is presented. Incidence rates (per 100,000 population) of lymphatic, unspecified (undifferentiated, giant cell and megakaryocytic subtypes), and myelogenous leukemia were determined for each age group. The rates for myelogenous leukemia were similar in all age groups and lower than those of lymphatic and unspecified leukemia which were approximately the same and characterized by a peak in the two-three year-old group. Statistical analysis of male:female ratios indicated no significant differences for the three types of leukemia or for the ages of onset. Graphing the incidence of the three subtypes of leukemia in children residing outside of New York City gave similar slopes only for the lymphatic and undifferentiated cases under two years old. Comparisons of slopes within cell types revealed significant difference only between the slopes of the incidence of acute lymphatic leukemia in the less than two years-old group and the four-nine year-old group. Implications of these analyses for the etiology of the childhood leukemias are considered.

4120 CANCER IN CHILDREN IN GREATER BOMBAY (1964-72): A COMPARATIVE STUDY. (Eng.) Jussawalla, D. J. (Bombay Cancer Registry, Indian Cancer Society, Bombay, India); Yeole, B. B.; Natekar, M. V. *Indian J. Cancer* 12(2):135-143; 1975.

Childhood cancers diagnosed in Bombay, India between 1964 and 1972 are reviewed and compared with the rate and type in other countries. During this period, 942 children under 15 (555 boys, 387 girls) were diagnosed as having cancer (3.0% of total cancer cases). About 42% of the children were under five years old. The age groups 5-9 and 10-14 shared the remaining cancer cases equally. Lymphatic and hematopoietic tissues accounted for 51.4% of all cancer cases in boys and 41.2% in girls. The next most commonly affected sites were the eyes, brain, and other parts of the nervous system. In the microscopically confirmed cases, sarcoma and retinoblastoma were the most common cancers in children under five. Gliomas, lymphomas and leukemias were equally distributed in the three age groups. The majority (88%) of Wilms' tumors were seen in children under five. Ewing's sarcoma (36.1%) and osteogenic sarcoma (41.7%) were the most common bone cancers. Fibrosarcomas were the most common connective tissue cancers (50%); Wilms' tumor constituted 77.8% of kidney cancers; retinoblastomas accounted for 90.7% of eye cancers; and gliomas accounted for 68.1% of brain cancers. Fifty percent of the lymphomas were lymphosarcomas, and 37.2% were Hodgkin's disease. In the leukemia cases, 48.1% were of lymphatic and 19.9% of myeloid origin. The incidence of cancer as well as mortality decreased with advancing age. Fifty-one cancer registers world-wide ranked according to age-adjusted incidence rates revealed only four having a lesser incidence in boys and five in girls, as compared with that of Greater Bombay.

4121 A GENETIC-EPIDEMIOLOGIC STUDY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE. I. STUDY DESIGN AND PRELIMINARY OBSERVATIONS. (Eng.) Cohen, B. H. (Johns Hopkins Univ. Sch. Hygiene and Public Health, 615 North Wolfe St., Baltimore, Md. 21205); Ball, W. C., Jr.; Bias, W. B.; Brashears, S.; Chase, G. A.; Diamond, E. L.; Hsu, S. H.; Kreiss, P.; Levy, D. A.; Menkes, H. A.; Permutt, S.; Tockman, M. S. *Johns Hopkins Med. J.* 137(3):95-104; 1975.

A large-scale (3390 subjects) genetic-epidemiologic investigation of chronic obstructive pulmonary disease was conducted to examine the role of several genetic and environmental factors, both singly and in combination, in the disease. The investigation consisted of two projects: (a): a modified case-control study in which biochemical, physiologic, demographic, personal, family, and sociobiological data were collected on pulmonary disease patients, several comparison groups, and selected family members; and (b) an ancillary project in which data similar to the first project were collected but more individuals per kindred were studed to examine intra- and inter-familial patterns. All subjects, patients, and relatives received pulmonary function tests, had blood and saliva samples collected, and were tested for the ability to taste phenylthiocarbamide. Pulmonary function tests included tests of pulmonary mechanics, gas distribution, diffusing capacity, and closing capacity. The $alpha_1$-antitrypsin determinations included electrophoretic phenotyping and serum trypsin inhibitory capacity. Typing of genetic markers (RBC antigens and enzymes, plasma proteins, and saliva markers) was used to determine associations and linkage relationships in detailed family studies. In all groups studied, cigarette smokers showed a higher frequency of pulmonary function abnormality than those who never smoked. There was a higher frequency of Pi variant phenotypes among patients with chronic obstructive pulmonary disease than among those without lung disease. First degree relatives of chronic obstructive pulmonary disease cases showed a significantly higher frequency of pulmonary function impairment than first degree relatives of nonpulmonary patients. The difference was still seen when Pi variant relatives and smokers were excluded, indicating that there is a familial component in pulmonary dysfunction that is not entirely due to Pi type or smoking. In the ABO blood group, there seemed to be a low frequency of blood group B among Caucasian patients with chronic obstructive pulmonary disease. No unusual patterns in Rh(D) frequency or in the occurrence of phenylthiocarbamide taste blindness were observed in either whites or blacks. It is suggested that an interaction of constitutional and extrinsic factors probably determines both clinical manifestations and disease progression.

4122 SIMILAR GEOGRAPHICAL DISTRIBUTION OF MULTIPLE SCLEROSIS AND CANCER OF THE COLON. (Eng.) Wolfgram, F. (Reed Neurol. Res.

Center, Univ. California, Los Angeles, Calif. 90024). *Acta Neurol. Scand.* 52(4):294-302; 1975.

A search was made of all diseases listed in the Annual Statistics of the World Health Organization (WHO) to determine if any disease had the same geographical distribution as multiple sclerosis. A list was made of the countries in which there was a significant mortality from multiple sclerosis as indicated by the WHO Annual Statistics for 1966-1970. All diseases with significant mortality rates (83 entries) were compared to the geographical distribution of multiple sclerosis. In the five years of this survey, 33,849 people died with multiple sclerosis in the 36 countries selected for study. The female/male mortality ratio was 1.33 for this period. Only cancer of the colon had essentially the same geographic distribution and female/male ratio as multiple sclerosis. There were 474,927 deaths from cancer of the colon during the survey years, and the female/male ratio for this was 1.25. The major exceptions to the parallel distribution between multiple sclerosis and cancer of the colon were Poland, Spain, Czechoslovakia and Portugal. Rectal cancer had a geographical distribution similar to that of multiple sclerosis and colonic cancer except that it was relatively high in Japan, and the female/male ratio was 0.85. Coronary heart disease had a relatively good correlation to the distribution of multiple sclerosis and cancer of the colon, but the female/male ratio was 0.74. Epidemiological evidence indicates that children born in western societies of Asian and African immigrant parents may be as susceptible to both multiple sclerosis and cancer of the colon as are the native-born Caucasian children. It is hypothesized that both multiple sclerosis and cancer of the colon have rather long latent periods in which pathogenic environmental factors are operative before clinical symptoms are manifest. It is suggested that a dietary disease would be plausible in explaining the long latent period and the susceptibility of immigrant children to both diseases.

4123 ENVIRONMENTAL FACTORS AND CANCER INCIDENCE AND MORTALITY IN DIFFERENT COUNTRIES, WITH SPECIAL REFERENCE TO DIETARY PRACTICES. (Eng.) Armstrong, B. (Radcliffe Infirm., Oxford, England); Doll, R. *Int. J. Cancer* 15(4):617-631; 1975.

Incidence rates for 27 cancers in 23 countries and mortality rates for 14 cancers in 32 countries were correlated with a wide range of dietary and other variables to determine relationships between these variables and cancer rates. Variables included in the study were liquid energy during 1955-1957; solid energy, 1955-1957; population density, 1965; tea consumption, 1955-1957; coffee, 1955-1957; cigarettes, 1963-1965; total fat; total protein; animal protein; calories; fats and oils; fish; eggs; meat; fruit; vegetables; pulses, nuts and seeds; sugar; potatoes, starchy and other staple foods; cereals; physician density, 1965; and gross national product. Product-moment simple and first-order partial correlation coefficients between the cancer rates and the environmental variables were calculated. The product-moment correlation method was used in preference to a rank correlation method as it provides the most satisfactory partial correlation coefficients. The intercorrelations between all the environmental variables were tabulated in the triangular form. This arrangement permits the identification of environmental variables that are highly correlated with one another. Dietary variables were strongly correlated with several types of cancer, particularly meat consumption with cancer of the colon and fat consumption with cancers of the breast and corpus uteri. Examination of a large number of environmental variables and the calculation of partial coefficients increases the probability that these associations are not just secondary to an association with some other variable. The data suggest that diet may have an effect upon many cancers, perhaps by affecting the metabolism of various carcinogens (as has been previously suggested), or by altering the body's capacity to deal with malignant cells.

4124 EPIDEMIOLOGICAL STRATEGIES FOR IDENTIFYING CARCINOGENS. (Eng.) Janerich, D. T. (Cancer Control Bureau, New York State Dept. Health, New York, N.Y.); Lawrence, C. E. *Mutat. Res.* 33(1): 55-63; 1975.

Two situations in which epidemiologic studies were used to identify carcinogens are reviewed and efforts to use New York State Cancer Control Bureau data for systematic surveillance of reported cancer incidence are discussed. The association between diethylstilbestrol and vaginal cancer in young women and between vinyl chloride and angiosarcoma of the liver was confirmed by epidemiological evidence, although in both cases the association was initially suggested by clinical observations. In the case of diethylstilbestrol, epidemiologic studies indicated the limits of the risk associated with intrauterine exposure; it is suggested that age limits will be identified for the carcinogenic potential of intrauterine exposure to diethylstilbestrol, just as intrauterine exposure to X-rays causes an increased risk of leukemia only during the first decade of life. In the case of vinyl chloride, its connection with angiosarcoma of the liver was first based on clinical observations and the rare nature of the disorder. Both of these situations indicate that present methods of detection are crude, and that a large number of people are exposed to chemicals before their carcinogenic potential is recognized. Preliminary efforts to develop a systematic cancer monitoring methodology in New York State involved analysis of cancer data from three anatomical sites: colon, pancreas, and gallbladder. These efforts yielded one instance in which an unquestionably high cancer incidence was suggestive of some environmental etiological agent. In two years, a single county showed unusual rates of pancreatic cancer. However, preliminary investigation showed no obvious environmental exposure associated with the cluster, and in subsequent years the incidence rate returned to within expected limits. Two alternatives in devising an epidemiological strategy are considered: the cohort study and the case history study. The case history study sometimes runs the risk of failing to detect a disease risk when one is actually

present. Even when a properly structured cohort study is done, it is only as precise as the sample size used in the study. It is concluded, however, that epidemiologic studies, together with laboratory and clinical disciplines, can produce a reasonable degree of assurance about the absolute limits of the risk associated with the use of suspected environmental hazards.

4125 FLUORESCENCE ASSOCIATED WITH CORN INFECTED WITH *ASPERGILLUS FLAVUS* AND *PARASITICUS* IN STORAGE. (Eng.) Rambo, G. (Purdue Univ., West Lafayette, Indiana 47907); Tuite, J.; Zachariah, G. L. *Cereal Chem.* 52(6):757-764; 1975.

The effects of moisture, temperature, and inoculation of *Aspergillus flavus* and *A. parasiticus* on the production of bright greenish yellow fluorescence (BGYF) and aflatoxin were investigated in corn. Two yellow dent corn hybrids were inoculated with the two *Aspergillus* species and stored in static and aerated systems. Both BGYF and blue white fluorescence (BWF) were observed under black light in the inoculated grain. The incidence of these fluorescences varied with each isolate in relation to storage conditions. The *A. parasiticus*-inoculated grain had more BWF than BGYF, whereas corn inoculated with *A.flavus* had similar amounts of both fluorescences. The correlation between the incidence of either the BGYF or BWF and aflatoxin in individual kernels was 74-80% for *A. parasiticus*, a good aflatoxin producer, but very low for *A.flavus*, a poor toxin producer. Aflatoxin occurred in 6.7 and 19.6% of the nonfluorescing kernels selected from the static and aerated tests, respectively. The BGYF test could be used as a basis for a rational selection of samples for aflatoxin assay in corn. BWF, because it occurs in nonviable kernels, may also be of use in screening for potential aflatoxin.

4126 MIGRANT STUDIES OF LUNG CANCER. (Eng.) Reid, D. D. (London Sch. Hygiene Tropical Medicine, London, England). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 319-322.

Statistics on lung cancer mortality rates of immigrants to the U.S. and to the British Isles are analyzed. A 1961 U.S. study reveals: (1) death rates of immigrant men are similar to those of men of the same age in the country of origin; (2) death rates of men in older age groups approach that of the new homeland; (3) death rates for women are much lower and the male-female ratio is closely related to the absolute mortality level of men. Similar conclusions can be drawn from a recent study of lung cancer in England and Wales on immigrant groups from the West Indies, India and Pakistan, as well as Europe, the U.S. and the British Commonwealth countries. The relationship of duration of smoking and the risk of death from lung cancer is discussed. Death rates in U.S. males correlate more closely with duration of smoking to the fourth power than with total cigarette consumption. The effect of environmental factors such as air pollution is considered to be minimal.

4127 OCCUPATIONAL LUNG CANCER AMONG COPPER SMELTERS. (Eng.) Kuratsune, M. (Faculty of Medicine, Kyushu Univ., Fukuoka, Japan). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 98-101.

Two epidemiological studies of occupational lung cancer are reported for: 1) workers in a large copper refinery and 2) workers in a small arsenic plant and the inhabitants of the small remote hamlet in which it was situated. A case control study was carried out using mortality cards filed in the health center serving the locality where the copper refinery was located. The case group consisted of 19 males who had died from lung cancer during 1967-1969; the control group consisted of 19 males randomly selected from deaths caused by diseases other than lung cancer. Cases and controls were matched for age, place and year of death. Occupational and nonoccupational history was obtained by family interviews. No significant difference was noted between the groups for most of the occupational items tested. However, 58% of the case group had been employees of the copper refinery compared to 37% of the controls. Of the case group, 58% had been copper smelters while only 16% of the control group were in this category. No significant difference was noted for nonoccupational history. These findings suggest that employment as smelters in the refinery was the main cause of the high lung cancer mortality seen among males of the town. Latent period ranged from 26-48 yr. All 11 cases were officially recognized as being caused by occupational exposure to arsenic and other compounds released during the smelting process. In the second study, all mortality cards kept at the health center which was responsible for the small hamlet in which the arsenic plant had been located were examined and 27 deaths from lung cancer were identified from the entire jurisdictional area during a 10-yr period. The control group consisted of 27 deaths randomly selected from deaths caused by diseases other than lung cancer. Of the lung cancer deaths seen in the whole jurisdictional area of the health center, 24% had lived in the town with the arsenic plant which comprises less than 1% of the population served by the health center. Similar significant differences were seen for employment at the arsenic plant but not for other occupational factors. These facts suggest that occupational and probably nonoccupational exposure to arsenic and other compounds released from the arsenic plant increased the incidence of lung cancer. It is concluded that heavy exposure to dusts and fumes released in the smelting of arsenic-containing ores greatly increases the risk of lung cancer.

4128 LUNG CANCER IN MEN: A MODEL FOR THE RELATIONSHIP BETWEEN AGE AT DIAGNOSIS AND SMOKING HABITS. (Eng.) Weiss, W. (3912 Netherfield Road, Philadelphia, Pa. 19129). *Am. Rev. Respir. Dis.* 111(6):883-886; 1975.

A model was constructed to determine the relation between age at diagnosis of lung cancer and smoking habits. A sizeable group of men with a birth spread of ten years who developed lung cancer which was diagnosed within a ten-year period were studied. Thus, the ages of the cancer cases were limited to a 19-yr spread. The multiplicity of birth cohorts and the small segment (only ten years over a 30-40 yr portion of the life span) of the life span distribution of cases observed were confounding and restraining conditions. The curve (age distribution *versus* number of deaths) suggests that a small degree of skewing in the age distribution of lung cancer cases in a ten-year period represents a larger shift in the actual life span age distributions. Thus, the constraint of the conditions causes a damping of the effect of shifts in life span age distribution.

4129 GEOGRAPHIC PATHOLOGY OF OCCULT THYROID CARCINOMAS. *(Eng.)* Fukunaga, F. H. (Kuakini Hosp., Honolulu, Hawaii 96817); Yatani, R. *Cancer* 36(3):1095-1099; 1975.

Because of the considerable variation in the reported prevalence of occult thyroid carcinomas, 1,167 thyroid glands obtained at autopsy from patients in various parts of the world were examined microscopically using identical techniques and diagnostic criteria. Specimens were obtained from patients in southeastern Canada, northeastern Japan, southern Poland, western Colombia, and from Japanese living in Hawaii; they were serially step-sectioned, and a carcinoma was classified as occult if it was less than 1.5 cm in diameter and unsuspected clinically. The criteria for the diagnosis of papillary carcinoma were pale cytoplasm, large vesicular- to ground glass-appearing nuclei with very prominent nuclear membranes that gave etched appearance. The prevalence of occult papillary thyroid carcinoma was significantly higher in Japan (28.4%) and in Hawaiian Japanese (24.2%) when compared with Canada (6%), Poland (9.1%), and Colombia (5.6%). The carcinomas were all papillary except for a single follicular lesion from Colombia. There was no significant sex prevalence. Most of the patients were 40-79 yr of age, but there was no predominant decade. Only the Colombian series had a large number of younger patients, and they showed a slightly lower prevalence of occult carcinomas before age 40. Most papillary thyroid carcinomas grow slowly and probably remain occult for the life of the patient.

4130 CELL KINETICS OF HUMAN SOLID TUMORS FOLLOWING CONTINUOUS INFUSION OF ^{3}H-TDR. (Eng.) Terz, J. J. (Medical Coll. Virginia, Health Sciences Div. Virginia Commonwealth Univ., Richmond, Va.); Curutchet, H. P. *Cell Cycle in Malig. Immun., Proc. Annu. Hanford Biol. Symp., 13th.* Richland, Washington, D.C., U.S. Energy Research and Development Administration, 1975, pp. 323-329.

The cell proliferation kinetics of four human solid tumors was analyzed following the administration of tritiated thymidine (^{3}H-TdR) *in vivo*. Four patients (epidermoid carcinoma of the maxillary antrum, recurrent epidermoid carcinoma of the neck, metastatic carcinoma of the pancreas, and carcinoma of the breast) received a continuous infusion of 2 mCi a day of ^{3}H-TdR for a period ranging from 6-20 days. Biopsies were obtained during and after the infusion period. In each case the mitotic index, labeling index, percent of labeled mitosis, and median grain count were determined. The duration of the cell cyle ranged between 18 hr (epidermoid carcinoma of the neck) to 6 days (adenocarcinoma of the pancreas). The size of the proliferating tumor-cell population rose to 30% at six days and to 60% in 20 days. Ninety percent of the mitoses were labeled at 20 days. In one patient, a simultaneous analysis of the cell kinetics of the normal tissue and tumor counterpart was performed. These studies suggest that a significant segment of the tumor-cell population (40%) does not divide (prolonged G_1 or G_0) at least for 20 days.

4131 THEORETICAL ASPECTS OF GROWTH FRACTION IN A G_0 MODEL. (Eng.) Burns, F. J. (New York Univ. Medical Center, New York, N.Y.). *Cell Cycle in Malig. Immun., Proc. Annu. Hanford Biol. Symp., 13th.* Richland, Washington D.C., U.S. Energy Research and Development Administration, 1975, pp. 315-322.

In a model of the cell cycle previously presented, the proliferating cells (P cells) were subdivided into a G_0 phase from which cells were released randomly at a rate consistent with the proliferation rate of the tissue as a whole and a C phase. The C phase received the cells released from the G_0 phase and was of uniform duration consisting of various subphases including the S phase and the G_2 phase. The model in this paper introduces a rate constant that describes the conversion of P_1 cells into nonproliferating cells (Q cells). The presence of Q cells requires that the growth fraction (GF) be less than 1. Cell loss was assumed to occur either uniformly from all the cells in the population (P cells and Q cells) or solely from the Q population. Expressions for the frequency-of-labeled-mitosis (FLM) curves, percentage of cells in the S phase, and the age distribution functions were derived in terms of GF, the proliferation rate, K_p, the loss rate, K_L, and the durations of the various C subphases. The results indicate that the ratio of the percentage of cells in the S phase to the plateau level of the damped FLM curve is GF/2. The model is fitted to experimental FLM curves of normal tissue (hamster cheek epithelium; intestinal crypt) and 15 tumors with diverse growth and cell-loss characteristics.

4132 SOME ASPECTS OF ERYTHROPOIETIC CELL PROLIFERATION IN ERYTHROLEUKAEMIA. (Eng.) Mitrou, P. S. (Zentrum der Inneren Medizin, Theodor-Stern-Kai 7, D-6000, Frankfurt 70, West Germany); Fischer, M.; Hubner, K. *Acta Haematol (Basel)* 53 (2):65-74; 1975.

Two questions are raised. Are proliferating ery-

throblasts arrested in a defined phase of the cell cycle? And have "megaloblastoid" erythroblasts any distinguishing proliferative characteristics? Single cell suspensions from the bone marrow of six patients were incubated in the presence of tritiated thymidine with a specific activity of 5 Ci/mM. Cell smears were fixed, stained, and photographed. Specific cell areas were marked with an 'Objektmarker'. May-Grünwald-Geimsa and Feulgen stains were used. DNA content was measured with a cytophotometer UMSP 1 at 560 nm. The mean DNA value for at least 40 lymphocytes represented the diploid value. Autoradiographs were prepared by the dipping method at 18 C on emulsion K5. Unstained smears were exposed for seven days at 2-4 C, while stained smears were exposed for 21 days. Unlabeled cells with diploid DNA were in the presynthetic phase (G_1); all labeled cells were in the S phase. Unlabeled cells with tetraploid DNA could be found in the premitotic phase (G_2). The cytophotometric, radiographic profile showed an abnormally increased percentage of basophilic erythroblasts and early polychromatic normoblasts in G_1 with a decrease in DNA synthesizing cells in four of the cases. In two cases "megaloblastoid" basophilic erythroblasts showed either a decrease during DNA synthesis or an increase in G_1, in contrast to morphologically normal cells. DNA labeling experiments indicated that "megaloblastoid" early polychromatic normoblasts are nonproliferating. Percentages of these cells in the smears decreased by as much as 90% between the G_1 and S phases.

4133 DECLINING MORTALITY AND IMPROVING SURVIVAL FROM WILMS' TUMOR. (Eng.) Everson, R. B. (Natl. Cancer Inst., Bethesda, Md.); Fraumeni, J. F., Jr. *Med. Pediatr. Oncol.* 1(1):3-10; 1975.

4134 OCCUPATION AND BOWEL CANCER. (Eng.) Berg, J. W. (Univ. Iowa Coll. Medicine, Iowa City, Iowa 52242); Howell, M. A. *J. Toxicol. Environ. Health* 1(1):75-89; 1975.

4135 ASBESTOS IN THE GREAT LAKES BASIN WITH EMPHASIS ON LAKE SUPERIOR. (Eng.) Anonymous (International Joint Commission -- United States and Canada). 98 pp., 1975. [available through National Technical Information Services, Washington, D.C. Document No. PB-240 134/7WP]

4136 A NEW METHOD FOR QUANTITATION OF AFLATOXIN IN CORN [abstract]. (Eng.) Seitz, L. M. (Grain Marketing Res. Center, Manhattan, Kansas 66502); Mohr, H. E. *Cereal Foods World* 20(9):442; 1975.

4137 AFLATOXIN: DISTRIBUTION IN CONTAMINATED, INSECT-DAMAGED CORN FRESHLY HARVESTED IN 1973 [abstract]. (Eng.) Shotwell, O. L. (Northern Regional Res. Lab., ARS, USDA, Peoria, Ill. 61604); Goulden, M. L.; Lillehoj, E. B.; Kwolek, W. F.; Hesseltine, C. W. *Cereal Foods World* 20(9):442; 1975.

4138 AN EVALUATION OF POTENTIAL MYCOTOXIN-PRODUCING MOLDS IN CORN MEAL. (Eng.) Bullerman, L. B. (Dep. Food Sci. Technol., Univ. Nebraska-Lincoln); Baca, J. M.; Stott, W. T. *Cereal Foods World* 20(5):248-250; 253; 1975.

4139 CYTOKINETIC MEASUREMENTS OF SPONTANEOUS C3H MAMMARY TUMORS [abstract]. (Eng.) Poulakos, L. (Allegheny Gen. Hosp., Pittsburgh, Pa.). *Proc. Am. Assoc. Cancer Res.* 16:25; 1975.

4140 BLOOD-VESSEL NEOPLASMS IN CHILDREN: EPIDEMIOLOGIC ASPECTS. (Eng.) Chabalko, J. J. (Epidemiology Branch, Natl. Cancer Inst., Bethesda, Md. 20014); Fraumeni*, J. F., Jr. *Med. Pediatr. Oncol.* 1(2):135-141; 1975.

4141 FAMILY HISTORY, PARITY AND ESTROGEN PRETREATMENT IN PATIENTS WITH BENIGN AND MALIGNANT BREAST LESIONS [abstract]. (Eng.) Black, M. M. (New York Medical Coll., New York, N.Y. 10029); Leis, H. P., Jr., Kwon, C. S. *Proc. Am. Assoc. Cancer Res.* 16:2, 1975.

4142 AN EPIDEMIOLOGIC STUDY OF OSTEOGENIC SARCOMA IN MALAYSIA. INCIDENCE IN URBAN AS COMPARED WITH RURAL ENVIRONMENTS AND IN EACH OF THREE SEPARATE RACIAL GROUPS, 1969-1972 [abstract]. (Eng.) Bovill, E. G., Jr. (Univ. California Sch. Medicine, San Francisco, Calif. 94110); Silva, J. F.; Subramanian, N. *J. Bone Joint Surg.* [*Am.*] 57A(7):1026; 1975.

4143 "FAMILIAL TUMORS" IN A MEDICAL ONCOLOGY PRACTICE [abstract]. (Eng.) Reimers, R. (Grand Rapids Oncol. Group, Mich.); Reimers, S.; Borst, J. R.; Moorhead, E. L., II. *Proc. Am. Assoc. Cancer Res.* 16:242; 1975.

4144 EPIDEMIOLOGICAL STUDIES OF EPSTEIN-BARR HERPESVIRUS INFECTION IN WESTERN AUSTRALIA. (Eng.) Lai, P. K. (Div. Microbiol., State Health Lab. Services, Western Australia); Mackay-Scollay, E. M.; Alpers, M. P. *J. Hyg. (Camb.)* 74(3):329-338; 1975.

4145 THE EPIDEMIOLOGY OF LUNG CANCER IN THE GERMAN FEDERAL REPUBLIC, WITH SPECIAL REFERENCE TO REGIONAL DIFFERENCES. (Ger.) Neumann, G. (7000 Stuttgart 1, Schickhardstr. 35, West Germany). *Prax. Pneumol.* 29(1):32-42; 1975.

4146 TRENDS IN LUNG CANCER MORTALITY IN ITALY. (Ita.) D'Alfonso, G. (Clinica Tisiologica, Universita di Napoli, Naples, Italy); Scarano, L. *Lotta Tubere. Mal. Polm. Soc.* 44(3):409-436; 1974.

4147 REPLICATION KINETICS OF HUMAN BREAST CANCER CELLS *IN VIVO* AND *IN VITRO* [abstract]. (Eng.) Post, J. (New York Univ. Res. Serv. Goldwater Mem. Hosp., Roosevelt Is., New York, N.Y.); Sklarew, R. J.; Hoffman, J. *Proc. Am. Assoc. Cancer Res.* 16:34; 1975.

See also:

* (Rev): 3605, 3606, 3608, 3610, 3613, 3623, 3627, 3628, 3629, 3630, 3640, 3642, 3643, 3647, 3648, 3660, 3661, 3662, 3663, 3664, 3665
* (Chem): 3670, 3716
* (Phys): 3771, 3773
* (Viral): 3807
* (Immun): 3899
* (Path): 4023, 4032, 4112

4148 ISOLATION OF CELL SUBPOPULATIONS FROM *IN VITRO* TUMOR MODELS ACCORDING TO SEDIMENTATION VELOCITY. (Eng.) Durand, R. E. (Dept. Radiology, Univ. Wisconsin, Madison, Wis. 53706). *Cancer Res.* 35(5):1295-1300; 1975.

Chinese hamster V79-171 cells grown *in vitro* as asynchronous single cells, as plateau-phase cultures, and as multicell spheroids contained subpopulations that differed in cell volume. These subpopulations could be isolated according to their sedimentation velocity at unit gravity. Asynchronous cells were found to sediment at a modal velocity of 17.7 mm/hr, whereas the modal sedimentation velocities of plateau and spheroid cells were 16.0 and 15.1 mm/hr, respectively. When the composition of each subpopulation was determined using either [^{3}H]thymidine incorporation or sensitivity to ionizing radiation as an index of cell cycle position, it was found that G_1-like populations developed in both *in vitro* tumor models. Since the sedimentation velocity technique permits isolation of functionally different cell subpopulations after treatment with cytotoxic agents, it may be possible to assay differential lethality when such agents are applied to cells growing *in situ* in a tumor-like situation.

4149 FAST- AND SLOW-GROWING TRANSPLANTABLE TUMORS DERIVED FROM SPONTANEOUS MAMMARY TUMORS OF THE DBA/2 Ha-DD MOUSE. (Eng.) Hosokawa, M. (Roswell Park Memorial Inst., Buffalo, N.Y. 14263); Orsini, F.; Mihich*, E. *Cancer Res.* 35(10): 2657-2662; 1975.

Nineteen transplantable tumor lines were established from individual spontaneous mammary tumors of the DBA/2 Ha-DD mouse. Of these lines, five were classified as fast growing, eight as medium growing, and six as slow growing, based on the time required for the tumors to reach a size of 10 mm in average diameter and on the average survival time of tumor-bearing syngeneic hosts. The relative differences in rate of growth among five of these lines remained stable during 11 to 19 transplant generations. In DBA/2J mice, a slow-growing and a fast-growing tumor line were cross-immunogenic. The differences in growth rate between these two tumor lines were not primarily related to differences in immunogenicity since they were not abolished in preirradiated hosts. The growth of cell populations from these two tumor lines in culture was comparable; however, cells from the fast-growing line had a plating efficiency about four times higher than those from the slow-growing line. The data are consistent with the possibility that fast-growing tumor lines have a higher incidence of cells with greater oncogenic potential than do slow-growing lines.

4150 SEQUENTIAL ANALYSIS OF TRANSPLANTABLE HEPATOCELLULAR CARCINOMAS. (Eng.) Becker, F. F. (New York Univ. Sch. Medicine, New York, N.Y. 10016); Wolman, S. R.; Asofsky, R.; Sell, S. *Cancer Res.* 35(11/Part 1):3021-3026; 1975.

The stability of transplantable hepatocellular carcinomas (THC) derived from animals fed N-2-fluorenylacetamide was studied. The ancuploid THC, 251a and 251c, remained relatively stable through 44 generations. THC 251c, a typical ancuploid tumor, grew rapidly, was very poorly differentiated histologically, showed a hypotriploid chromosomal mode, and produced large quantities of plasma proteins and α_1F. All the diploid THC remained moderately well differentiated histologically and none produce plasma proteins or α_1F. During the initial transplant generations a slow drift to a higher modal number of chromosomes was observed. THC 252 was carried as 3 separate sublines. Each of the sublines showed parallel evolution with a modal range of 42 to 46 chromosomes in the 2nd transplant and a mode at 44-45 by the 10th transplant generation. Little further change through the 23rd generation was seen. A fast growing variant arose spontaneously from the diploid tumor 252 at the 16th generation. The sudden karyotypic evolution in this tumor variant was characterized by increase in tetraploidy and both stable and unstable chromosomal rearrangements. Only the stable rearrangements persisted, and marker chromosomes were common to all of the metaphase cells examined after further transplantations. Despite the striking cytogenetic alterations and a current growth rate of 2.5 weeks, this tumor produces neither plasma proteins nor α_1F. The failure of the variant subline to produce any detectable plasma proteins or α_1F indicates that synthesis of these proteins is strongly associated with the original karyotype of the primary tumor.

4151 INFLUENCE OF UREMIA ON THE PROLIFERATION KINETICS OF A SOLID TRANSPLANTABLE CARCINOMA. (Ger.) Feaux de Lacroix, W. (Pathologisches Institut der Universitat, D-5000 Koln 41, Joseph-Stelzmann-Str. 9 West Germany); Clemens, A.; Klein, P. J.; Castrup, H. J.; Lennartz, K. J. *Beitr. Pathol.* 155(4):410-427; 1975.

The effect of uremia (corresponding to a blood urea level of 133 mg%) on the proliferation kinetics of partially differentiated mammary carcinoma HB was studied in 316 C_3H/Tif adult female mice by autoradiography. The study began on the 21st day after tumor transplantation, or seven days after uremia induction. Uremia was induced by ligation of the right ureter and by infarction of two-thirds of the left kidney. The starvation effect was avoided by additional tube feeding. The growth of the tumor was reduced by uremia. The tumor doubling time was increased from 7.5 days in untreated and sham-operated animals to 15 days in uremic mice. This was due mainly to a reduction of the growth fraction from about 50% to 20%, and to a prolongation of the regeneration time from 15.5 to 19 hr as a result of the prolongation of T_{G1} phase. The cell loss factor was constant at about 81% in all groups. The findings are similar to those previously obtained for the epithelium of the stomach, intestine, and skin, as well as for erythroblasts.

4152 CONTROL OF CELL DIVISION IN THE CORNEA OF RATS. III. MITOGENIC EFFECT OF ISOPROTERENOL AND THEOPHYLLINE. *(Eng.)* King, C. D. (Univ. of Tennessee Center for the Health Sciences, Memphis, Tenn. 38163); Kauker, M. L.; Cardoso, S. S. *Proc. Soc. Exp. Biol. Med.* 149(4):840-844, 1975.

The individual and combined effects of isoproterenol (10 or 25 mg/kg, ip) and theophylline (50 or 100 mg/kg, ip) on the circadian mitotic rhythm and rates of cell division within the corneal epithelium were studied in male Holtzman rats. The rats were sacrificed at various intervals after drug treatment, and the number of mitoses per eye were counted microscopically. Isoproterenol at 25 mg/kg produced an initial suppression of cell division during the period when high rates of cell division were observed in the untreated controls (0700 hr); this suppression was followed by a rise in mitotic activity with a peak at 2200 hr (corresponding to the control nadir) and a subsequent decline in activity after 0100 hr. At 10 mg/kg, isoproterenol produced an initial inhibition of cell division (0700 hr) followed by a peak at 1300 hr, a trough at 1900 hr, and a second peak at 2300 hr. Theophylline at 100 mg/kg produced an initial suppression of cell division (0700 hr), followed by a peak at 1300 hr, a nadir at 1900 hr, and a second peak at 2300 hr. At 50 mg/kg, the alterations in circadian rhythm were similar to those seen with 10 mg/kg isoproterenol. When isoproterenol (10 mg/kg) and theophylline (50 mg/kg) were given together, the late evening-early morning peak of cell division was greatly magnified over the effects produced by either drug alone. In addition, the suppression in cell division seen 24 hr after drug administration with all drug treatments was greatly magnified after combined drug treatment. Isoproterenol, but not theophylline, caused a temporary tachycardia and hypotension. It appears unlikely that the cardiovascular responses to isoproterenol play a major role in the activation of cell division.

4153 SELECTION OF CELL LINES RESISTANT TO CYCLIC AMP AND THEOPHYLLINE FROM MOPC 173 MURINE PLASMOCYTOMA: CROSS-RESISTANCE TO OUABAIN AND CONCANAVALIN A. (Fre.) Paraf, A. (Institut de Biologie Moleculaire CNRS, Universite Paris-VII, 2, place Jussieu, 75005 Paris, France); Faivre, E.; Zilberfarb, V.; Lelievre, L.; Zachowski, A. *C. R. Acad. Sci.* [D] *(Paris)* 281(10):683-685; 1975.

Using cyclic AMP (cAMP) and theophylline as selective agents, variants resistant to the specific actions of both these substances were obtained from two strains (ME_2N sensitive to, and MF_2N insensitive to contact inhibition) of cells from MOPC 173 murine plasmacytoma. The strains were also resistant to other drugs (ouabain and concanavalin A) which are supposed to act at the level of the plasma membrane. The cAMP selection developed resistance to cAMP (50 times for ME_2N, 5 for MF_2N) much more than to another drug (ouabain: two to four times for ME_2N and MF_2N; concanavalin A: two for ME_2N). Selection by a specific inhibitor (ouabain) seems to entail the appearance of variants comparable to those that can be obtained with drugs the active site of which is not well known (cAMP or theophylline) but also with the selective action of concanavalin A which acts at the surface of the cell. It is thought that certain membrane enzymes are associated into complexes with coordinated action; this would explain the appearance of a crossed resistance. Because of this coordinated action, there would only be a restricted number of membrane conditions, all others being lethal. This would imply that, whichever the effector, one or more enzymatic reactions is often modified either directly or indirectly. In simple cases where the specificity of the action is known (eg, ouabain, Mg^{++}, Na^{+}, K^{+}, ATPase) three hypotheses can explain the pleiotropic modification observed in the resistant variants: an enzyme mutation which modifies the affinity of the drug for the enzyme and the interactions of the enzyme with the lipid environment, a mutation of a membrane protein which is distinct from the enzyme which acts as a regulator by coordinating a number of enzymatic activities, and a modification of the regulator gene that may interfere with the lipid constituents of the membrane.

4154 THE FAILURE OF METHOTREXATE TO INHIBIT CHICKEN FIBROBLAST PROLIFERATION IN A SERUM-CONTAINING CULTURE MEDIUM. (Eng.) Mitchell, R. S. (Univ. Colorado Medical Center, Denver, Colo. 80220); Balk*, S. D.; Frank, O.; Baker, H.; Christine, M. J. *Cancer Res.* 35(9):2613-2615; 1975.

Methotrexate (1 μM) abolished the proliferation of chicken fibroblasts in the plasma-containing medium with supplemental folic acid but was without effect when the medium contained serum. The serum and defibrinogenated plasma (both from chickens) did not differ significantly in folate content. The serum contained more than 10 times as much thymidine as the plasma, suggesting that the release of preformed DNA precursors from the formed elements of blood during the clotting process is responsible for the phenomena observed.

4155 CYCLIC AMP AND CELL MORPHOLOGY IN CULTURED FIBROBLASTS: EFFECTS ON CELL SHAPE, MICROFILAMENT AND MICROTUBULE DISTRIBUTION, AND ORIENTATION TO SUBSTRATUM. (Eng.) Willingham, M. C. (Natl. Cancer Inst., Bethesda, Md. 20014); Pastan, I. *J. Cell Biol.* 67(1):146-159; 1975.

The ultrastructural changes induced by N^6, $O^{2'}$-dibutyryl cyclic adenosine 3',5' monophosphate (Bt_2cAMP) in 3T3-4 and L929 cells, and the additional effects that Bt_2cAMP exerted on the orientation of 3T3 cells to their substratum, were studied. The change in shape of 3T3 and L929 cells due to 1mM Bt_2cAMP treatment for 24 hr was accompanied by altered intracellular distribution of microfilaments and microtubules. Bt_2cAMP added to cells in low density culture caused (a) microfilaments to accumulate in bundles near the plasma membrane, mainly at the cell periphery, and (b) microtubules to accumulate beneath these microfilament bundles. In narrow cell processes which formed characteristically in Bt_2cAMP-treated L cells, microtubules accumulated in parallel arrays near the center of these processes.

A new simple method for evaluating the relative distance of the cell from its underlying substratum was used. The method involves the diffusion of toluidine blue into blocks of cells embedded *in situ* in Epon; 2-3 hr incubation at 60-80 C are required for the stain to diffuse completely through the single layer of cells adjacent to the surface of the block. At various times the blocks are removed and washed in H_2O, and the cell components that have been stained up to that time are observed with light microscopy and photographed. In this way, those components of the cell closest to the block surface, and hence the former substratum, are stained first, followed later by staining of components farther away.

4156 CYCLIC AMP AND THE MALIGNANT TRANSFORMATION OF CELLS. (Eng.) Pastan, I. (Natl. Cancer Inst., Bethesda, Md.). *Adv. Metab. Disord.* 8:377-383; 1975.

Cyclic AMP (cAMP) levels in mouse 3T3 and normal rat kidney cells and their virus-transformed derivatives were measured during early logarithmic growth and when the cells were crowded together. In logarithmically growing normal cells, cAMP concentrations varied directly with the doubling time, i.e., rapidly growing cells had low concentrations and slow growing cells had high cAMP levels. Normal cells had elevated cAMP levels when growth ceased, while levels remained low in transformed cells as the latter grew to high densities. Treatment of transformed cells with cAMP derivatives or agents that raise cAMP levels (dibutyryl cAMP, theophylline, prostaglandin E_1) restored morphology to normal, increased adhesiveness, decreased motility and agglutinability by plant lectins, and slowed growth. Specific activities of adenylate cyclase and cAMP phosphodiesterase in NRK cells increased as the cells multiplied and then diverged as the cells crowded together. Adenylate cyclase continued to rise; the phosphodiesterase remained unaltered or fell slightly. In four kinds of transformed cells, adenylate cyclase activity remained low even when the cells were closely crowded together. The cells were NRK cells transformed by Kirsten sarcoma virus and Moloney sarcoma virus and chick embryo cells transformed by the Bryan High Tier strain and the Schmidt Ruppin strain of Rous sarcoma virus. Low cAMP levels in transformed cells are apparently due to diminished adenylate cyclase activity, which may be related to transformation-induced alterations in plasma membrane components. The inability of the cells to maintain normal cAMP levels may account for their increased growth rate, increased agglutinability by plant lectins, altered morphology, decreased adhesiveness to substratum, and enhanced motility.

4157 MODULATION OF THE DISTRIBUTION OF PLASMA MEMBRANE INTRAMEMBRANOUS PARTICLES IN CONTACT-INHIBITED AND TRANSFORMED CELLS. (Eng.) Furcht, L. T. (Dept. Lab. Medicine and Pathology, 488 Jackson Hall, Univ. Minnesota, Minneapolis, Minn. 55455); Scott, R. E. *Biochim. Biophys. Acta* 401(2):213-220; 1975.

The intrinsic organization of the plasma membrane in normal and transformed cells was studied with the technique of freeze fracture and electron microscopy. Contact-inhibited 3T3 cells were shown to contain aggregated plasma membrane intramembranous particles, while simian virus 40- transformed 3T3 cells demonstrated a uniform particle distribution. The distribution of intramembranous particles in transformed cells was affected by colchicine or vinblastine (10^{-7}-10^{-5} M) which induced a dose- and time-dependent particle aggregation. These observations suggest that microtubules and other membrane-associated colchicine-sensitive proteins probably influence the distribution of intrinsic membrane proteins and intramembranous particles in nucleated mammalian cells. An aggregated particle distribution was observed in 3T3 cells or colchicine-treated transformed cells frozen in media, phosphate-buffered saline or following brief exposure to glycerol, sucrose or dimethyl sulfoxide containing solutions, independent of whether specimens were rapidly frozen from 37 C, room temperature or 4 C incubations. Cells briefly stabilized in 1% formaldehyde yielded similar patterns of particle distribution as cells rapidly frozen in media or in cryoprotectants. Glutaraldehyde fixation of cells, however, appeared to alter the fracturing process in these cells, as visualized by an altered fracture face appearance, decreased numbers of particles, and no particle aggregates. Differences in membrane organization between normal and transformed cells were therefore demonstrated using a series of preparative methods, and colchicine and vinblastine were shown to modulate intramembranous particle distribution in transformed 3T3 cells.

4158 NONMALIGNANCY OF HYBRIDS DERIVED FROM TWO MOUSE MALIGNANT CELLS. II. ANALYSIS OF MALIGNANCY OF LM(TK^-) Cl 1D PARENTAL CELLS. (Eng.) Jami, J. (Institut de Recherches Scientifiques sur le Cancer, Boite Postale 8, 94800 Villejuif, France); Ritz, E. *J. Natl. Cancer Inst.* 54 (1):117-122; 1975.

The possibility that the Cl 1D cell line, an L-cell line derivative, was a mixture of malignant and nonmalignant cells was investigated because previous experiments showed that some hybrids derived from Cl 1D and tumor cell lines grew *in vivo*, whereas others apparently did not have that capacity. More highly malignant Cl 1D cells were not selected by animal passage of tumors obtained from inoculation of cultures. Only 10% of immunologically intact syngeneic C3H and semiallogeneic $C3D2F_1$ and $D2C3F_1$ mice inoculated sc with 1 million or more Cl 1D cells developed tumors. The tumor-producing capacity of this line was increased to 81% in mice X-irradiated (350 R) one day before injection, and 1×10^3 cells were sufficient to produce tumors. These observations suggested that the low capacity of Cl 1D cells to grow *in vivo* did not result from varying degrees of malignancy but mainly from interference of immunogenetic factors between cells and their inbred hosts of origin. Numerous hybrids between tumor and host cells were in all tumors examined.

4159 PROLIFERATION OF MONONUCLEAR PHAGOCYTES (KUPFFER CELLS) AND ENDOTHELIAL CELLS IN REGENERATING RAT LIVER: A LIGHT AND ELECTRON MICROSCOPIC CYTOCHEMICAL STUDY. *(Eng.)* Widmann, J. J. (Anatomisches Institut der Universitat, Im Neuenheimer Feld 307, 69 Heidelberg, West Germany); Fahimi*, H. D. *Am. J. Pathol.* 80(2):349-366, 1975.

The mitotic potential and possible origin of Kupffer cells was investigated in regenerating rat liver after partial hepatectomy using endogenous peroxidase and uptake of large (0.8 μ) latex particles as markers of Kupffer cells. Female albino rats (Charles River strain) were subjected to two-thirds partial hepatectomy and sacrificed 1-11 days after surgery, using four rats for each time interval. Thirteen hours prior to sacrifice, each animal received an iv injection of 0.05 ml/100 g of 0.81 μ latex particles, followed one hour later by 1 mg vinblastine to arrest the dividing cells in mitosis. Livers were fixed by perfusion, and pieces of tissue were processed for cytochemical localization of endogenous peroxidase activity in Kupffer cells. From each animal, 10-15 1-μ-thick sections stained with 1% toluidine blue were examined by light microscopy, and dividing sinusoidal cells with and without peroxidase activity were localized. The corresponding tissue blocks were examined by electron microscopy. The sinusoidal cells exhibited a marked regenerative response after partial hepatectomy. Peroxidase activity persisted in endoplasmic reticulum of Kupffer cells during mitosis. Latex particles were exclusively localized in such peroxidase-positive cells, thus confirming their identity as Kupffer cells. Quantitative counts revealed that the peak mitotic activity of Kupffer cells occurred at 48 hr, whereas that of endothelial cells was at 96 hr after partial hepatectomy. These findings indicate that Kupffer cells are capable of dividing locally in the liver; no morphologic evidence of transformation of endothelial cells or monocytes to Kupffer cells was found. It is concluded that the Kupffer cells are formed predominantly by local cell division after partial hepatectomy in the model of liver regeneration. These observations have established the usefulness of endogenous peroxidase and latex-labeling as markers of Kupffer cells.

4160 CRITIQUE OF THE "CRITICAL MASS" HYPOTHESIS OF THE REGENERATION OF LIVER CELLS. *(Eng.)* Tongendorff, J. (Max-Planck-Institut fur Biochemie, 8033 Martinsried bei Munchen, West Germany); Trebin, R.; Ruhenstroth-Bauer*, G. *Am. J. Pathol.* 80(3): 519-524, 1975.

Johnson's hypothesis that the regulation of liver cell regeneration is triggered by the critical mass of the cells was examined mathematically and experimentally. The mathematical expression of the "critical mass" theory is intended to describe the rate sequence of the mitotic response of a regenerating liver. However, it does not take into account the increase in cell number and correlative distribution of cell volume in the regenerating liver. Due to this defect, the mathematical treatment of Johnson is untenable as the heuristic demonstration for the applicability of the "critical masses" theory. To check the applicability of the total theory to liver regeneration *in vivo*, four volume distributions of 10,000 individual liver cells from female BDE-inbred rats were determined at various intervals after two-thirds hepatectomy. In histologic liver sections, the respective mitotic index was evaluated by counting 10,000 hepatocytes of each sample. The analysis of the volume distributions of hepatocytes and of the rates of mitosis registered after partial hepatectomy showed markedly variable values for the alleged "critical volume." The fact that the "critical volume" theory is not sufficient to explain the mitotic regulation of liver regeneration was also shown by the experimental results, indicating that the initial cell hypertrophy that is normally observed is not a necessary condition for cell division. Thus, both the mathematical considerations and the experimental results show that Johnson's "critical mass" theory is not suitable for use in describing the regulation of liver regeneration.

4161 THE CONTENT OF UNBOUND POLYAMINES IN BLOOD PLASMA AND LEUKOCYTES OF PATIENTS WITH POLYCYTHEMIA VERA. (Eng.) Desser, H. (Ludwig Boltzmann Institut fur Leukaemieforschung und Hamatologie, Hanuschkrankenhaus, Heinrich Collinstrasse 30, A-1140 Vienna, Austria); Hocker, P.; Weiser, M.; Bohnel, J. *Clin. Chim. Acta* 63(3): 243-247; 1975.

Putrescine, spermidine, and spermine concentrations were determined in the blood plasma and isolated WBC of 11 patients with polycythemia vera and in three healthy subjects. The polyamines were analyzed on a chromatography column filled with the ion-exchange resin PA-35. The average values in the WBC of the healthy volunteers were found to be 1.8 ± 1.4 nM putrescine/10^8 cells, 3.0 ± 0.9 nM spermidine/10^8 cells and 12.9 ± 3.8 nM spermine/10^8 cells. In the plasma of healthy persons the amounts of the polyamines were below the sensitivity level of the method employed. In four patients with polycythemia vera no polyamines were detected. However, in seven cases 0.1-3 nM polyamines/ml were found. The level of polyamines in the WBC of six of these patients was decreased, and in one patient corresponded to the values found in the normal range (17.7 ± 6.0 nM polyamines/10^8 cells). Continued blood-letting therapy on three patients led to values approaching the concentrations found in normal subjects in both blood plasma and WBC. A decreased amount of these diamines in the WBC of the patients was seen to correlate with an elevated concentration in the plasma.

4162 ACCUMULATION OF POLYAMINES AFTER STIMULATION OF CELLULAR PROLIFERATION IN HUMAN DIPLOID FIBROBLASTS. (Eng.) Heby, O. (Univ. California Medical Center, San Francisco, Calif.); Marton, L. J.; Zardi, L.; Russell, D. H.; Baserga, R. *Cell Cycle in Malig. Immun., Proc. Annu. Hanford Biol. Symp., 13th.* Richland, Washington, D.C., U.S. Energy Research and Development Administration, 1975, pp. 50-66.

The cellular content of the polyamines putrescine,

spermidine, and spermine was studied at various intervals after confluent monolayers of WI-38 human diploid fibroblasts were stimulated to synthesize DNA by replacing exhausted medium with medium containing 10% fetal calf serum. Spermine was the quantitatively dominating polyamine. In unstimulated cells, spermine content was four times that of spermidine and 18 times that of putrescine. Upon stimulation, a 6-fold increase in putrescine content was observed. The accumulation of putrescine preceded the onset of DNA synthesis and coincided with peak of synthesis of ribosomal RNA. The magnitude of putrescine accumulation depended on the percentage of cells that were stimulated to proliferate. The cellular content of spermidine and spermine increased subsequently to that of putrescine. However, within one hour after stimulation, there was an increase in spermidine content, followed by a gradual decrease. During the remainder of the prereplicative phase, the spermidine content was within the same range as that of unstimulated cells. The activity of putrescine-activated S-adenosyl-L-methionine decarboxylase showed a similar pattern, i.e., an increase within two hours, a depression at about eight hours, and an increase during the period of DNA synthesis. The early stimulation of spermidine synthesis coincides with the increased synthesis of nonhistone chromosomal proteins, the marked rise in chromatin template activity for RNA synthesis, and the increased incorporation of ^{3}H-uridine into the RNA of whole cells, which have been previously shown to occur within the first few hours after stimulation.

4163 DECREASED ^{3}H-URIDINE INCORPORATION AND INCREASED ^{3}H-ADENOSINE INCORPORATION BY HeLa CELLS EXPOSED TO AUTOLOGOUS CULTURE FLUID. (Eng.) Tilley, R. (Medical Coll. Georgia, Augusta, Ga. 30902); Nair*, C. N. *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):359-368; 1975.

The ^{3}H-uridine (^{3}H-UR) and ^{3}H-adenosine (^{3}H-AR) incorporation of actively growing HeLa monolayer cultures briefly exposed to the culture fluids (CF) from confluent HeLa cultures was measured. Exposure to CF inhibited the uptake as well as the incorporation of ^{3}H-UR by cultures; less ^{3}H-UR was incorporated in the CF-exposed cultures than in control cultures similarly exposed to fresh medium and labeled. The inhibition of ^{3}H-UR incorporation by CF-exposed cultures could be reduced by increasing the concentration of ^{3}H-UR in the labeling medium. ^{3}H-AR uptake was increased in the CF-exposed cultures. Both the inhibition of ^{3}H-UR incorporation and the stimulation of ^{3}H-AR incorporation were prevented by washing the CF-treated cultures with phosphate-buffered saline before labeling. Similarly, both effects could be producted in HeLa cultures exposed to fresh medium containing 1×10^{-5} M uridine instead of to CF. Therefore, the observed effects of CF on label incorporation were probably due to the presence of uridine or a related compound, and the inhibition of ^{3}H-UR incorporation resulted from reduced uptake of ^{3}H-UR rather than from reduced RNA synthesis by exposed cells. The active agent in the CF, formed only when cultures were incubated at physiological temperatures (34-37 C) and not at 45 C, was not a product of medium decay. It was a cellular product formed equally well by cultures incubated in medium containing dialyzed or whole serum, indicating that it was present in calf serum.

4164 AGING OF HUMAN FIBROBLASTS *IN VITRO*: SURFACE FEATURES AND BEHAVIOR OF AGING WI 38 CELLS. (Eng.) Bowman, P. D. (Div. Natural Sciences, Thimann Lab., Univ. California, Santa Cruz, Calif. 95064); Daniel, C. W. *Mech. Ageing Dev.* 4(2):147-158; 1975.

WI38 cells at various *in vitro* ages and a simian virus 40-transformed variant were examined by ^{3}H thymidine autoradiography, time lapse cinematography and scanning electron microscopy. There was a good correlation between cellular morphology, behavior, and the ability to incorporate ^{3}H thymidine in normal WI38 cells. Small, elongate spindle-shaped cells were usually both active incorporators of ^{3}H thymidine, as determined autoradiographically, and they divided actively as determined by time lapse cinematography. Larger, more spread out cells tended to be nondividers. The proportion of large, nondividing cells increased with increasing *in vitro* age and was correlated with changes in cell surface and behavior. Transformed WI38 cells exhibited no such changes as a function of age. The results support the thesis that *in vitro* aging reflects the inability of individual cells to undertake DNA synthesis and to complete division, but nondividers continue to enlarge and unusual sizes and shapes are attained.

4165 EFFECTS OF WITHDRAWAL OF A SERUM STIMULUS ON THE PROTEIN-SYNTHESIZING MACHINERY OF CULTURED FIBROBLASTS. (Eng.) Mostafapour, M.-K. (Dept. Biology, Massachusetts Inst. Technology, Cambridge, Mass. 02139); Green, H. *J. Cell. Physiol.* 86(2/Suppl. 1/Part II):313-319; 1975.

3T6 cells resting in medium containing 0.5% serum were stimulated to prepare for multiplication by the addition of medium containing 10% serum. After a number of hours, when the rate of preribosomal RNA synthesis, total RNA content (mainly ribosomal), and the cytoplasmic content of poly A (a measure of poly A(+) mRNA) were considerably elevated, the serum-rich medium was withdrawn, and the original medium replaced. The rate of preribosomal RNA synthesis began to drop within 30 min, but required a much longer time to fall to a new resting level. When the serum-rich medium was withdrawn after 12 hr of stimulation, the total RNA content required 12-18 hr to fall to the resting level, whereas cytoplasmic poly A content and the rate of protein synthesis declined more rapidly, reaching a new resting level within eight hr. During the 12 hr following withdrawal of the serum-rich medium an appreciable fraction of the cells initiated DNA synthesis. Presumably, the cellular preparations for DNA synthesis cannot be immediately reversed because of the inertial factors related to the protein-synthesizing machinery.

4166 INDEPENDENCE OF SIALIC ACID LEVELS IN NORMAL AND MALIGNANT GROWTH. (Eng.) Khadapkar, S. V. (Cancer Res. Inst., Tata Memorial Centre, Parel, Bom bay 400 012, INdia); Sheth, N. A.; Bhide, S. V. *Cancer Res.* 35(6):1520-1523; 1975.

Sialic acid content in breast or tumor tissue and in serum of mouse strains that are either susceptible (C3H/J) or resistant (C57BL) to breast cancer was measured at various age periods. Sialic acid content was also studied in normal lung tissue and in lung adenoma and hepatoma. Sialic acid levels during nonmalignant growth of a tissue were measured in breast tissue during pregnancy and lactation, and in regenerating liver, as well as in newborn and postnatal liver. The sialic acid content, when expressed per milligram of protein, increased in mammary tumor, lung adenoma, and hepatoma. It also increased in nonmalignant growth of breast tissue during pregnancy and lactation and of regenerating liver and postnatal liver. Increase in sialic acid per milligram DNA was observed only in lung tumors, regenerating liver, and postnatal liver. It appears that the changes in sialic acid level are independent of the normal or malignant growth of a tissue and that these changes might be the function of the parameter used to express the sialic acid values, i.e., either the DNA content or protein content of a given tissue.

4167 CYTOCHEMICAL AND ULTRASTRUCTURAL STUDIES CONCERNING THE CELL COAT GLYCOPROTEINS IN NORMAL AND TRANSFORMED HUMAN BLOOD LYMPHOCYTES. II. COMPARISON OF LANTHANUM-RETAINING CELL COAT COMPONENTS IN T AND B LYMPHOCYTES TRANSFORMED BY VARIOUS KINDS OF STIMULATING AGENTS. (Eng.) Anteunis, A. (INSERM U. 104, Hopital Saint-Antoine, Paris 12, France); Vial, M. *Exp. Cell Res.* 90(1):47-55; 1975.

The lanthanum colloidal technique and electron microscopy were used to study the modifications occurring during blast formation in the composition and amounts of the lanthanum-retaining surface components of human blood T and B lymphocytes. Cells harvested from human blood samples were incubated with phytohemagglutin (PHA-P) (0.02 μg/ml), concanavalin A (Con A) (25 μg/ml), anti-human-lymphocyte horse immunoglobulin (Ig) (ALS, 0.06 mg/ml), tuberculin (25 μg/ml), or goat antisera directed against human $F(ab')_2$ and Fc fragments as well as against human γ, α, μ, δ, and ε intact heavy chains (1/20 dilution). In mixed lymphocyte reactions (MLR), lymphocytes were incubated with mitomycin-C-treated lymphocytes from a genetically unrelated donor. Control cell suspensions consisted predominantly of small lymphocytes, most of which showed a thick continuous electron-opaque layer external to the membrane. This lanthanum-retaining material (LRM) was shown to be a fuzzy zone of varying width surrounding the whole surface of single cells. Subsequent to mitogen or MLR stimulation, the lymphocytes consisted of two broad categories of blast cells: immunoblasts (T-derived cells) and plasmablasts (B-derived cells). The PHA-, Con A-, ALS-, tuberculin-, and MLR-stimulated lymphocytes usually exhibited lanthanum-positive figures which were thinner than those observed in the controls. In addition, the outer zone of the cell coat showed regular cone-shaped deposits of high electron density. The tuberculin- and MLR-stimulated cultures showed less positive patterns. The LRM was markedly decreased in cells incubated with anti-Ig sera directed against human $F(ab')_2$ and Fc fragments. Cells incubated with anti-Ig sera directed against the δ, μ, and ε heavy chains showed a thin, more or less continuous, electron-opaque external layer of varying density and width; treatment with anti-γ-chain and anti-α-chain sera led to weakly positive or no lanthanum staining. The physicological significance of the lanthanum alterations remains uncertain.

4168 GLYCOPROTEIN DIFFERENCES BETWEEN THE ASCITES AND CULTURED FORMS OF THE SARCOMA 180 TUMOR. Huggins, J. W. (Dept. Biochemistry, Oklahoma State Univ., Stillwater, Okla. 74074); Chestnut, R. W.; Durham, N. N.; Carraway, K. L. *Biochem. Biophys. Res. Commun.* 65(2):497-502; 1975.

The cell surface glycoproteins of sarcoma 180 tumor cells grown *in vitro* in cell culture or *in vivo* as an ascites form in mice were examined by periodate-Schiff staining of sodium dodecyl sulfate acrylamide gels and by lactoperoxidase labeling. The cells were cultured in McCoy's 5a modified medium, and the ascites cells were grown in the peritoneal cavity of mice. The cells grown in culture showed the presence of a set of surface membrane glycoproteins which were absent or markedly decreased in the ascites form. Conversely, the ascites form had a glycoprotein that was not evident in the cells in culture. The other surface membrane polypeptides and enzyme activities were essentially the same for the two cell types. The glycoprotein differences may be related to the ability of the cells to interact with each other or a substratum.

4169 C-REACTIVE PROTEIN IN MALIGNANT TUMOURS. (Eng.) Baruah, B. D. (Assam Medical Coll., Dibrugarh, Assam, India); Gogoi, B. C. *Indian J. Cancer* 12(1):39-45; 1975.

To evaluate its potential in the diagnosis and prognosis of cancer, C-reactive protein was quantitatively analyzed in the sera of 100 patients with different malignant tumors, 30 patients with benign tumors, and 30 normal individuals. The C-reactive protein was determined using the quantitative latex fixation test with anti-C-reactive protein reagent. The erythrocytic sedimentation rate was estimated using Westergren's method. The C-reactive protein test was negative in all of the normal individuals (16 males and 14 females aged 15-50 yr); the erythrocytic sedimentation rate in these subjects ranged from 2-8 mm/hr in the males and from 5-15 mm/hr in the females. In the benign tumor group, the C-reactive protein test was negative in all patients except one with fibroleiomyoma of the uterus, and the erythrocytic sedimentation rate was within the normal range in all cases except two with fibroleiomyoma of the uterus. Both the positivity and titer of C-reactive protein increased according to the extent of the disease in the

malignant tumor group. Higher titers were observed in patients with sarcomas, lymphomas, and late carcinomas. Lower titers were observed in leukemia and the test was negative in one case of multiple myeloma. The erythrocyte sedimentation rate tended to vary according to the C-reactive protein titer. No appreciable change in C-reactive protein was observed during telecobalt therapy or chemotherapy despite clinical improvement. However, C-reactive protein became negative within about three weeks after radical surgery. Following early aggressive treatment, C-reactive protein disappeared completely from the blood, its reappearance during reactivation of the disease occurring before the disease became clinically apparent. The results indicate that the C-reactive protein test may be useful in differentiating benign free malignant tumors and in monitoring patients for recovery from or reactivation of malignant disease.

4170 HISTONE CONSERVATION IN NORMAL AND HERITABLY DAMAGED MURINE LEUKAEMIC LYMPHOBLASTS L5178Y-S. (Eng.) Szumiel, I. (Dept. Radiobiology and Health Protection, Inst. Nuclear Res., ul. Dorodna 16; 03-195 Warszawa, Poland); Budzicka, E.; Beer, J. Z. *Acta Biochim. Pol.* 21(3):299-304; 1974.

Histone turnover was examined in the fast-growing murine leukemic lymphoblast line, L5178Y-S, and in a slowly growing subline, A651/3, isolated from an X-irradiated L5178Y-S culture. Cells were cultured as suspensions in Fischer medium supplemented with 8% calf serum. Protein labeling was performed by culturing cells in medium containing 0.17 μCi/ml L-[1-^{14}C]leucine, and DNA labeling was accomplished with medium containing 0.1 μCi/ml [6-^{3}H]-thymidine. Histones were separated by polyacrylamide gel electrophoresis. After cells were transferred to nonradioactive medium, the specific radioactivity of L5178Y-S histones decreased at a rate of 0.0581, which was not significantly different from the predicted rate of 0.0626. After electrophoretic separation of the histones, the four fractions were found to decrease at a rate not significantly different from that of the total histone. Likewise, the specific radioactivity of A651/3 histones declined at a rate of 0.0478, not significantly different from the predicted rate of 0.0435. The rate of DNA radioactivity decline was found to be practically the same as that for histones. It is suggested that histone molecules are conserved in the chromatin. X-irradiation, which results in the heritable damages of the proliferative ability, does not change the stability of histones.

4171 RATE AND TIME OF DNA SYNTHESIS OF INDIVIDUAL CHINESE HAMSTER CELLS. (Eng.) Dormer, P. (Inst. Hamatologie, 8 Munchen 2, Landwehrstr. 61, West Germany); Brinkmann, W.; Born, R.; Steel, G. G. *Cell Tissue Kinet.* 8(5):399-412; 1975.

The applicability, limitations, and sources of error of a new technique for measuring the rate of DNA synthesis of individual cells were investigated. In addition, a comparative study by the FLM method was presented. Using the diploid cell line B14FAF28 Chinese hamster fibroblasts, the rate of DNA synthesis was measured by means of quantitative autoradiography following a short-term incubation of the cells with 5 x 10^{-6} M fluorodeoxyuridine (FUdR) and 10^{-5} M [^{14}C]-thymidine (^{14}C-TdR). Grains over individual cells were counted using an incident light microphotometer. The direct measurements of DNA synthesis rate were statistically converted into "flux" parameters for comparison with the FLM method. The rate of ^{14}C-TdR incorporation revealed an inconstant rate of DNA synthesis throughout the S-phase. Seventy-three cells examined had a median ^{14}C-TdR incorporation rate of 21 x 10^{-18} M/cell/min, with a coefficient of variation of 13.9%. In experiments using exponentially growing cells, a median DNA synthesis time of 6.4-6.6 hr was obtained by the FLM technique, while a value of 6.0-6.1 was derived from the rate of synthesis. The determination of the mean duration of the S-phase in Chinese hamster cells by the two independent methods thus showed good agreement. The correlation of cellular DNA content with thymidine labeling produced no evidence of unlabeled cells having a DNA content characteristic of S-phase cells. While the coefficient of variation of the distribution of DNA synthesis ranged from 28 to 33%, the sources of variations were acknowledged. The major advantages of the new method are its establishment *in vitro* and the requirement of only one tissue sample.

4172 NUCLEOLAR RNA SYNTHESIS IN THE LIVER OF PARTIALLY HEPATECTOMIZED AND CORTISOL-TREATED RATS. (Eng.) Schmid, W. (Institut fur Zellforschung am Deutschen Krebsforschungszentrum Heidelberg, Heidelberg, West Germany); Sekeris, C. E. *Biochim. Biophys. Acta* 402(2):244-252; 1975.

RNA synthesis by isolated nucleoli from male Wistar BR II rat liver was measured 12-14 hr after partial hepatectomy and four hours after cortisol (30 mg/kg, ip) administration. RNA synthesis was increased significantly in these animals over controls. The increased RNA synthetic capacity was also demonstrable in the respective high salt nucleolar extracts and in Biogel A-1.5 filtration fractions of the nucleolar extracts. DNA saturation experiments, using nucleoli and Biogel fractions from control and treated animals as RNA polymerase source, demonstrated that saturation of transcription was reached at the same concentration of exogenous template; this was independent of the extent of RNA synthesis. It is concluded that the activity, and not the amount of nucleolar RNA polymerase, is increased as a result of partial hepatectomy or cortisol administration. Parallel to the effects on RNA polymerase, the activity of RNA-degrading enzymes present in nucleoli was also enhanced by the same treatment.

4173 THE ISOLATION AND CHARACTERIZATION OF GLYCOPEPTIDES AND MUCOPOLYSACCHARIDES FROM PLASMA MEMBRANES OF NORMAL AND REGENERATING LIVERS OF RATS. (Eng.) Akasaki, M. (Faculty Pharmaceutical Sciences, Kyoto Univ., Kyoto 606, Japan);

Kawasaki, T.; Yamashina, I. *FEBS Lett.* 59(1):100-104; 1975.

Glycopeptides and mucopolysaccharides were isolated from plasma membranes of normal and regenerating livers of male Wistar rats; the results were compared with previously published information on hepatoma membranes. Livers from normal rats were homogenized and centrifuged several times before the final pellet was suspended in a small volume of medium, and the suspension was separated through a sucrose gradient. The membranes obtained at the interphase between the cushion and the gradient were collected, washed, and lyophilized, yielding 0.50 mg protein/g liver. Plasma membranes from regenerating livers were obtained from rats that had been 70% hepatectomized. Some of the hepatectomized rats were injected ip three hours prior to death with 80 μCi[^{3}H]glucosamine (to label hexosamines and sialic acid), and with 200 μCi[^{35}S]Na_2SO_4 (to label *O*- and *N*-sulfates of mucopolysaccharides. Plasma membranes were prepared according to the procedure used for normal livers, with a yield of 0.37 mg protein/g liver. Lipids were extracted from the lyophilized plasma membranes, and the membranes were digested with pronase. Mucopolysaccharides were identified using cellulose acetate electrophoresis. Normal and regenerating livers gave similar glycopeptide patterns, all of which were apparently *N*-glycosidic and acidic in contrast to the production of both *N*- and *O*-glycosidic glycopeptides from the hepatoma membranes. The occurrence of heparan sulfate was common to all the plasma membranes from the livers and hepatomas. The presence of *O*-glycosidic glycopeptides in hepatomas having the capacity to grow in randomly bred rats, and their absence in tissue-specific hepatocytes appears to be consistent with a previously published suggestion that *O*-glycoproteins (the parent molecules which produce *O*-glycosidic glycopeptides on proteolytic digestion) may be involved in masking histocompatibility antigens at the cell surface.

4174 A HEPATOMA-ASSOCIATED ALKALINE PHOSPHATASE, THE KASAHARA ISOZYME, COMPARED WITH ONE OF THE ISOZYMES OF FL AMNION CELLS. (Eng.) Higashino, K. (Osaka Univ. Medical Sch., Osaka, Japan); Kudo, S.; Ohtani, R.; Yamamura, Y.; Honda, T.; Sakurai, J. *Ann. N.Y. Acad. Sci.* 259:337-346; 1975.

A comparative study was made among alkaline phosphatase isozymes of hepatoma, FL cells (derived from human amniotic membrane) and a 40-wk-old fresh amniotic membrane. FL cell alkaline phosphatase isozymes were separated by polyacrylamide gel electrophoresis. The dialyzed butanol extract of FL cells contained two main alkaline phosphatase isozymes; the fast moving band corresponded electrophoretically to hepatoma alkaline phosphatase. Amnion alkaline phosphatase differed from hepatoma and FL cell alkaline phosphatase isozymes in electrophoretic mobility. When the effects of L-phenylalanine, L-leucine, and L-homoarginine on the activity of alkaline phosphatase isozymes were compared, the inhibition pattern of the hepatoma alkaline phosphatase was similar to that of FL cell alkaline phosphatase and different from that of amnion alkaline phosphatase. Hepatoma alkaline phosphatase and the fast-moving FL cell alkaline phosphatase were inhibited only slightly and to the same extent by inorganic phosphate, whereas amnion alkaline phosphatase was very sensitive. The amnion alkaline phosphatase maintained its full activity during heat treatment at 65 C. The slow-moving FL cell alkaline phosphatase was more heat-stable than were the rest of isozymes. The hepatoma alkaline phosphatase and the fast-moving FL cell alkaline phosphatase behaved quite similarly against heat treatment and were less stable. The pH optima and Michaelis constants for phenyl phosphate were not significantly different for these isozymes. Ouchterlony double diffusion tests indicated that hepatoma alkaline phosphatase and the fast-moving FL cell alkaline phosphatase are antigenically indistinguishable. It is not yet known which type of alkaline phosphatase, the hepatoma or the placental type, occurs in the membrane in the early stage of pregnancy but changes during development. It may be regulated by the mechanism that controls the gene expression of the alkaline phosphatase isozymes in the amnion cells. It is suggested that a similar regulatory mechanism may operate in human carcinoma, which decides the preferential occurrence of either the Regan isozyme or the hepatoma alkaline phosphatase. This may explain the clinical finding that the hepatoma alkaline phosphatase occurs exclusively in hepatocellular carcinoma, while the Regan isozyme occurs preferentially in cancers other than hepatoma.

4175 TUMOR-SPECIFIC ALKALINE PHOSPHATASE IN HEPATOMA. (Eng.) Suzuki, H. (First Dept. Internal Medicine, Faculty of Medicine, Univ. Tokyo, Tokyo, Japan); Iino, S.; Endo, Y.; Torii, M.; Miki, K.; Oda, T. *Ann. N.Y. Acad. Sci.* 259:307-320; 1975.

The enzymic and immunological properties, tissue of origin, and clinical significance of human hepatoma alkaline phosphatase were examined. Eleven samples of hepatoma and adjacent uninvolved liver specimens of the mucosa from the intestines of three patients were also obtained at autopsy. Ten fetal livers and intestines (8-24 wk gestation) were obtained; and three placentas, amnions, and chorions were obtained at delivery. Three amnion cell lines were also studied. All tissues were homogenized and extracted in n-butanol; the aqueous extract was precipitated, dissolved in buffer, and the enzyme was separated by disc polyacrylamide gel electrophoresis. α-Fetoprotein and hepatitis B antigen were detected by radioimmunoassay. Eight active bands of serum alkaline phosphatase were observed by polyacrylamide gel disc electrophoresis, with one of these being designated hepatoma alkaline phosphatase. Hepatoma alkaline phosphatase was observed in 16 of 51 cases with hepatocellular carcinoma (31%); it was negative in hepatoblastoma, yolk sac tumor, and congenital bile duct atresia (in which α-fetoprotein was positive), and also in liver diseases such as chronic hepatitis and liver cirrhosis. No correlation was observed between α-fetoprotein and hepatoma alkaline phosphatase. He-

patoma alkaline phosphatase was observed in 2 of 4 cases in which serum α-fetoprotein was negative, indicating that they are produced independently. Hepatoma alkaline phosphatase was observed in 8 of 16 cases (50%) with positive hepatitis B antigen and was negative in 8 of 32 cases with negative hepatitis B antigen (28%). Histochemical examination of liver and tumor sections of the autopsied cases indicated that hepatoma alkaline phosphatase is localized within the hepatoma cells. The phosphatase was relatively heat-stable and sensitive to L-phenylalanine, and was immunologically different from placental and intestinal alkaline phosphatases. Among the alkaline phosphatases in the fetal organs, intestinal alkaline phosphatase showed properties that are close to hepatoma alkaline phosphatase, but the zymograms differed slightly. The electrophoretic mobility of hepatoma alkaline phosphatase coincided with that of the fast-moving bands of two of the amnion cell lines and its heat stability and sensitivity against L-phenylalanine were similar to those of these two cell lines; this suggests that hepatoma alkaline phosphatase is a carcino-placental protein.

4176 ATPase ACTIVITY OF NEUROBLASTOMA CELLS IN CULTURE. (Eng.) Ledig, M. (Centre de Neurochimie du CNRS, and Institut de Chimie Biologique, Faculte de Medicine, 67085 Strasbourg Cedex, France); Ciesielski-Treska, J.; Cam, Y.; Montagnon, D.; Mandel, P. *J. Neurochem.* 25(5):635-640; 1975.

Mouse neuroblastoma C1300 cells were grown in Dulbecco's medium, and the activity of Mg^{2+}- and Na^{+}-K^{+}-ATPase was determined. To induce the differentiation of the cells, 1 mM dibutyryl cyclic AMP (diB-cAMP) or insulin (0.3 U/ml) were added to the growth medium. To induce expansion growth, fetal calf serum was omitted. ATPase was measured indirectly as the inorganic phosphate (Pi), which was determined by spectrophotometry. The Na^{+}-K^{+}-ATPase activity corresponded to the difference between the Pi measured in the presence and absence of 1 mM ouabain in the incubation medium while the Mg^{2+}-ATPase corresponded to the Pi liberated in the presence of ouabain. The Na^{+}-K^{+}- and Mg^{2+}-ATPase activities of primary cultures were, respectively, 3 and times higher during proliferation in the stationary phase than in homogenates. In the absence of serum, expansion growth was accompanied by a 50% increase in Na^{+}-K^{+}-ATPase activity, which decreased to the level of the stationary phase by the second day. In the presence of diB-cAMP, the Na^{+}-K^{+}-ATPase activity of clone M1 increased by 74% on the second day, while Mg^{2+}-ATPase activity increased by 48% on the third day. In the absence of serum, Na^{+}-K^{+}- ATPase activity increased only when the cell density was less than 1.5 mg protein/75 cm^2. The increase in Na^{+}-K^{+}-ATPase activity was associated with the growth of long neuron-like processes. It is suggested that the decrease in activity after the second day of differentiation could be related to the increase in protein content of the cells or selection of cells having a lower activity. Likewise, the decrease in ATPase activities when cell density was high may be the result of contact inhibition, since cell processes were short when clustered. Thus, the results show the presence of ATPase associated with plasma membranes and an increase in this activity when long neuron-like processes appear.

4177 CHARACTERIZATION OF A NONHEPATIC ALCOHOL DEHYDROGENASE FROM RAT HEPATOCELLULAR CARCINOMA AND STOMACH. (Eng.) Cederbaum, A. I. (Mount Sinai Sch. Medicine, New York, N.Y. 10029); Pietrusko, R.; Hempel, J.; Becker, F. F.; Rubin, E. *Arch. Biochem. Biophys.* 171(1):348-360; 1975.

Ethanol oxidation by the soluble fraction of rat hepatoma 252 was compared to that of the liver. The tumor had been induced in a male ACI rat by administration of *N*-2-fluorenylacetamide. The hepatoma was transplanted into normal rats by sc or ip injection; since the rats bearing the tumors still had a normal liver, hepatoma and liver supernatant fractions were prepared from the same rat, the latter serving as a control for the former. Experiments were carried out on tumors that had undergone 14-18 passages. Ethanol oxidation by 100,000 x *g* liver and hepatoma supernatants was NAD-dependent, and the addition of pyrazole reduced the total steroidal reductase activity by 40-50%, suggesting the presence of alcohol dehydrogenase. At low concentrations of ethanol (10.8 mM) the alcohol dehydrogenase activities of hepatoma and liver supernatant fractions were comparable. When the concentration of ethanol was raised to 108 mM, the activity of the liver enzyme decreased by about 50%, whereas the activity in hepatoma supernatant fractions was elevated about 4-fold. With 1.3 mM *m*-nitrobenzaldehyde, the reducing activity was 32 times higher in hepatoma fractions than that in normal liver. By contrast the ability to metabolize 5-β-dihydrotestosterone (0.115 mM) and cyclohexanone (12.7 mM) was less than that in supernatant fractions of the liver. Electrophoresis of the liver supernatant fractions on ionagar at pH 7.0 revealed only one component that oxidized ethanol. Hepatoma supernatant fractions contained two components with alcohol dehydrogenase activity; one with the same electrophoretic mobility as the liver enzyme, the other showing a slower rate of migration. The latter component, which was absent in the liver, is designated hepatoma alcohol dehydrogenase. By electrophoresis on starch gels at pH 8.5, it could be demonstrated that the liver and hepatoma enzymes moved in opposite directions. The overall substrate specificity characteristics were similar to those of the liver enzyme in that the effectiveness of substrates increased with an increase in chain length and introduction of unsaturation or an aromatic group. Both liver and hepatoma alcohol dehydrogenase cross-reacted with antibody to horse liver alcohol dehydrogenase EE. The Michaelis constant for ethanol with the hepatoma enzyme was found to be 223 mM, compared to 0.3 mM for liver alcohol dehydrogenase; at 1.0 M ethanol the hepatoma enzyme was not fully saturated with substrate. The Michaelis constant for 2-hexene-1-ol was 0.3 mM, indicating that the hepatoma enzyme is better suited for dehydrogenation of longer chain alcohols. Stomach alcohol dehydrogenase was also found to have kinetic properties comparable

to those of the hepatoma enzyme, as well as similar electrophoretic mobility. In addition, the hepatoma enzyme was detected in the serum of rats bearing hepatomas.

4178 STUDIES ON TYROSINE HYDROXYLASE IN NUEROBLASTOMA, IN RELATION TO URINARY LEVELS OF CATECHOLAMINE METABOLITES. (Eng.) Imashuku, S. (Dept. Pediatrics, Kyoto Prefectural Univ. Medicine, Kawaramachi, Kamikyoku, Kyoto, Japan); Takada, H.; Sawada, T.; Nakamura, T.; LaBrosse, E. H. *Cancer* 36(2):450-457; 1975.

Tyrosine hydroxylase (TH) activity was determined in 22 neuroblastoma tumors from 15 patients, in one pheochromocytoma, 20 adrenal glands, ten other tumors and organs, and four specimens of sera. The enzyme activity was found only in the neural crest tumors and adrenal glands, but the levels were too low to be detected in the other tumors and in normal liver and kidney tissues. The average specific activity of TH in 23 neural crest tumors was 0.559 $\pm$ 0.101; in 20 adrenal glands was 0.418 $\pm$ 0.124 nM/mg protein/min. In 13 patients with neuroblastoma, and in the patient with pheochromocytoma, both TH levels in the primary tumors and urinary excretion of vanillylmandelic acid (VMA) and homovanillic acid (HVA) were studied. The urinary excretion of VMA by 10 of 13 neuroblastoma patients, and by the patient with pheochromocytoma, was significantly to markedly elevated above normal levels; excretion of HVA by 12 of 13 neuroblastoma patients was similarly elevated. These results indicate that tyrosine hydroxylase, an enzyme specifically located in the adrenal medulla and monoaminergic neurons, is also present in neuroblastoma, a malignant tumor of similar embryologic origin, and in pheochromocytoma. Not only can TH activity in these tumors be demonstrated *in vitro*, but the elevated urinary excretion of VMA and/or HVA by the majority of patients with these tumors also indicates TH activity of the tumors *in vivo*.

4179 THE HISTOCHEMICAL DEMONSTRATION OF ARYLSULPHATASE IN HUMAN TUMOURS. (Eng.) Koudstaal, J. (Dept. Pathology, "S.S.D.Z.", Stichting Samenwerking Delftse Ziekenhuizen, Reynier de Graefweg 7, Delft, The Netherlands). *Eur. J. Cancer* 11(11):809-813; 1975.

The activity of arylsulfatase in human tissues and malignant tumors was studied. The enzyme histochemical method with 6-bromo-2-naphthyl sulphate gave the best results of the substrates tested. Cells of the stratum granulosum and of the sheath of the hairfollicles of the skin showed a moderate enzyme activity. The strongest activity was seen in the proximal tubules of the kidney. Cells of the ductus epididymis possessed clear activity. Except for a trace in the corpus luteum, the human ovaries showed no enzyme activity. The placenta had activity in the syncytic- and cytotrophoblast cells. The adrenals showed some activity in the medulla. Generally, the enzyme activity of malignant tumors was very low, and decreased compared with the activity of normal corresponding cells. A clear enzyme activity was noted in 38 of the 62 colonic-rectal carcinomas. Thirty of the 62 carcinomas of the colon and rectum showed an increased activity compared with the neighboring non-tumorous epithelium. Some carcinomas of the stomach had increased activity. Some other tumors showed a clear enzyme activity: 4 mammary carcinomas, 2 renal carcinomas, 1 pancreas carcinoma, 1 hepatocellular carcinoma, 2 carcinomas of the endometrium, 1 carcinoma of the ovary, 2 testis tumours and 3 malignant melanomas. Nonepithelial tumours generally showed no enzyme activity.

4180 EFFECT OF ESTROGEN ON SYNTHESIS OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE IN R3230AC MAMMARY TUMORS AND UTERI. (Eng.) Ringler, M. B. (Univ. Rochester Sch. Medicine and Dentistry, Rochester, N.Y. 14642); Hilf*, R. *Biochim. Biophys. Acta* 411(1):50-62; 1975.

The effect of estrogen on synthesis of glucose-6-phosphate dehydrogenase in the R3230AC mammary adenocarcinoma of ovariectomized (seven days prior to experiments) Fischer rats was investigated. Enzyme synthesis was estimated by techniques using immunochemical precipitation and isolation of enzyme protein from tissues of rats that had been given radioactive leucine prior to sacrifice. The antibody-enzyme complex was dissociated and glucose-6-phosphate dehydrogenase was isolated after electrophoresis on sodium dodecyl sulfate-acrylamide gels. Administration of estradiol-17β produced a 2-fold increase in glucose-6-phosphate dehydrogenase activity, which was preceded by a 5-fold increase in specific synthesis of glucose-6-phosphate dehydrogenase in R3230AC tumors. At least a 15-fold increase in enzyme synthesis was observed in the uterus. The rate of enzyme degradation in the tumor was estimated at 17 hr. These data indicate that the estrogen-induced increase in glucose-6-phosphate dehydrogenase activity was due to a *de novo* increase in enzyme synthesis.

4181 UPTAKE OF NORADRENALINE BY AN ADRENERGIC CLONE OF NEUROBLASTOMA CELLS. (Eng.) Zwiller, J. (Centre de Neurochimie, Faculté de Médecine, 11, rue Humann, 67085 Strasbourg Cedex, France); Treska-Ciesielski, J.; Mack, G.; Mandel, P. *Nature* 254(5499):443-444; 1975.

Noradrenaline (NA) uptake was investigated in the androgenic clone MI isolated from C-1300 neuroblastoma cells. Cells were placed in a phosphate buffered saline medium (PBS) and observed for effects induced by amphetamine, desipramine, imipramine and ouabain on the NA uptake. Results elucidated two components when neuroblastoma cells were plotted against amine concentrations. The high affinity component (K_{m1} of 0.14 μM) was obtained in low concentrations of NA, while the low affinity component (K_{m2} , 2 x 10^{-5} M) was obtained in high NA concentrations. The uptake of NA was inhibited by 2,4-dinitrophenol when administered in the high concentrated medium. NA uptake was decreased in both components at 4 C. Ouabain inhibited the high affinity uptake of NA but did not affect the low affinity process. Imipramine and desipramine in-

hibited NA uptake for NA only in the high affinity process. This study postulates that NA uptake by androgenic neuroblastoma clones may represent a useful system for the study of catecholamine transport across the neuronal membrane.

4182 DIFFERENTIAL EFFECTS OF GLUCOCORTICOIDS ON DNA SYNTHESIS IN NORMAL AND VIRUS-TRANSFORMED CHICK EMBRYO CELLS. (Eng.) Fodge, D. W. (Dept. Molecular Biology and Virus Lab., Univ. California, Berkeley, Calif. 94720); Rubin, H. *Nature* 257(5529):804-806; 1975.

The effects of glucocorticoids on DNA synthesis in chick embryo cells are described. Cells were treated with varying concentrations of dexamethasone, hydrocortisone, and corticosterone for 16 hr. During this time the DNA synthesis was measured by the incorporation of [^{3}H]-thymidine (^{3}H-TdR) into DNA by autoradiography. All three glucocorticoids reduced incorporation of ^{3}H-TdR into DNA 4-6-fold. Levels of 1.5×10^{-10} M dexamethasone, 4.5×10^{-10} M hydrocortisone and 1.5×10^{-9} M corticosterone which are within the physiological concentration range of glucocorticoids, caused 50% inhibition of DNA synthesis. DNA synthesis was inhibited in the presence of serum within four hours of the administration of hydrocortisone and became more pronounced with time up to ten hours. In contrast, DNA synthesis was restored within four hours upon removal of the hydrocortisone. Glucose transport was measured by the uptake of [^{3}H]-2-deoxy-D-glucose (^{3}H-2dGlc). ^{3}H-2dGlc uptake was inhibited more rapidly than ^{3}H-TdR incorporation, but the extent of inhibition after 16 and 24 hr was similar. Hydrocortisone in concentrations as high as 1.0×10^{-5} M had no effect on DNA synthesis in cultures of chick embryo fibroblasts transformed by injection with Rous sarcoma virus. Glucocorticoids act by slowing the progress of cells through the G_1 phase of the cell cycle.

4183 SOME ASPECTS OF THE HORMONAL REGULATION OF CELLULAR FUNCTION. (Eng.) Pitot, H. C. (McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, Wis.). *Proc. Int. Cancer Congr. 11th.* Vol. 1 *(Cell Biology and Tumor Immunology).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 95-99.

Mechanisms by which hormones regulate macromolecular syntheses are discussed. Messenger RNA is now an accepted intermediate in the expression of genetic information in mammalian organisms as well as other forms of higher animals and plants. As to the subsequent fate of the messenger RNA, three possible pathways are suggested: it may be synthesized then degraded without ever being translated; there is evidence that some messenger RNA molecules are synthesized and translated for a relatively short time then degraded; and a considerable portion of the messenger RNA may be stabilized within the cytoplasm of the cell and then translated for extended periods of time. In nonreplicating systems there is considerable evidence that the final enzyme is degraded after it completes a certain functional life period. Assuming that some messenger RNA molecules in mammalian systems have a high degree of stability, one must conjecture that the regulation of genetic expression by hormonal systems may occur at the level of genetic translation. Various experiments point to the quite probable possibility that hormones exert their effects at two different levels of genetic expression: at the level of transcription; and at the level of the translating unit, the polysome. In neoplastic tissues, especially the liver, it is clear that many if not the majority of hormonal mechanisms regulating genetic expression are abnormal when compared with their normal cell of origin *in vivo*. It remains to be determined whether these mechanisms are predominantly defective at the level of genetic translation or at the level of genetic transcription.

4184 CULTURE OF ZOLLINGER-ELLISON TUMOR CELLS. (Eng.) Lichtenberger, L. M. (Univ. California Los Angeles Sch. Med.); Lechago, J.; Dockray, G. J.; Passaro, E., Jr. *Gastroenterology* 68 (5/Part 1):1119-1126; 1975.

The molecular form of gastrin synthesized and secreted by six Zollinger-Ellison tumors in culture was studied; the tumors were successfully grown *in vitro* by a monolayer tissue culture technique. The initial gastrin concentration in the medium varied between 0 and 100 ng/ml. Many cytoplasmic secretroy granules were seen in the cells of one culture population. Gastrin secretion was stimulated by the addition of fresh medium to the cultures. Both the culture cells and the medium contained primarily big gastrin (G-34), but smaller amounts of little gastrin (G-17) were also present. Since G-17 was the major molecular form in the original tumor tissue, it is postulated that an enzyme that breaks G-34 down to G-17 is normally present in tumor tissue but has a diminished activity in an *in vitro* environment. Gastrin concentration in the medium decreased with time in culture until no hormone was detected between 2 and 6 wk, possibly because of endocrine cell dedifferentiation and an increased proportion of fibroblasts in the population.

4185 PITUITARY AND SERUM CONCENTRATIONS OF PROLACTIN AND GH IN SNELL DWARF MICE. Sinha, Y. N. (Scripps Clinic and Res. Foundation, La Jolla, Calif. 92037); Salocks, C. B.; Vanderlaan, W. P. *Proc. Soc. Exp. Biol. Med.* 150(1): 207-210; 1975.

Secretions of prolactin and growth hormone (GH) in mutant dwarf mice (dw/dw) were studied using homologous radioimmunoassays. Blood samples from 12-13 adult male and female dw/dw mice were collected by orbital puncture and by decapitation. Compared to related normals (+/?), pituitary concentrations of prolactin were very low in dw/dw mice ($P<0.01$); males had only 35 ng prolactin/mg pituitary tissue and females had only 5 ng/mg in comparison with 1.3 and 4.4 μg/mg in respective controls. GH was 9.6 and 1.8 μg/mg for male and female dw/dw mice, respectively, compared to 67.8 and 37.5 μg/mg in

respective controls. Prolactin and GH concentrations were also lower in sera of dw/dw mice, but the relative differences appeared sex-dependent; serum GH was more reduced in males than in females, while serum prolactin was more depressed in females. The data confirm earlier indications of deficiencies in the circulating levels of prolactin and GH in dwarf mice and suggest that the hypoactivity of these hormones may be crucial to some of the anomalies found in this mutant.

4186 FIBROBLAST GROWTH FACTOR: ITS LOCALIZATION, PURIFICATION, MODE OF ACTION, AND PHYSIOLOGICAL SIGNIFICANCE. (Eng.) Gospodarowicz, D. (The Salk Inst. Biological Studies, San Diego, Calif.); Rudland, P.; Lindstrom, J.; Benirschke, K. *Adv. Metab. Disord.* 8:301-335; 1975.

Cell fibroblast growth factor (FGF), a homogeneous polypeptide hormone, has recently been isolated from bovine pituitary glands and from the brain of vertebrates. The purification, physical properties, and biological activities of the two peptides are reported with emphasis on pituitary FGF. The two peptides have the same apparent molecular wt (13,000) but differ in their *N*-terminal, which is lysine for pituitary FGF and is blocked for brain FGF. Whether obtained from the brain or pituitary glands, FGF was able to provoke division of cells as diverse as fibroblasts, chondrocytes, adrenal cells, endometrial cells, and glial cells obtained from bovine, murine, and human sources. Studies with 3T3 cells showed that FGF plus hydrocortisone could replace serum for provoking the initial events of cell division and that cells grown to confluency in the presence of 10% serum could be further stimulated to divide by the addition of FGF alone or FGF plus dexamethasone. In polyoma virus-transformed 3T3 cells, the growth-initiating ability of FGF was lost at permissive temperatures. The polypeptide was also shown to increase intracellular cyclic guanosine monophosphate levels in quiescent cultures of BALBc 3T3 cells and to control the pleiotypic responses of the cultures. *In vivo* experiments indicated that FGF could be one of the neurotrophic agents responsible for amphibian limb regeneration. FGF treatment of amputated limb stumps of adult frogs resulted in large deposits of undifferentiated cells resembling a regenerating blastoma. In some cases, differentiation of large masses of chondrocytes and muscle fibers was observed.

4187 PURIFICATION OF A FIBROBLAST GROWTH FACTOR FROM BOVINE PITUITARY. (Eng.) Gospodarowicz, D. (Salk Inst. Biological Studies, San Diego, Calif. 92112). *J. Biol. Chem.* 260(7):2515-2520; 1975.

The isolation of a fibroblast growth factor (FGF) from bovine pituitary extracts is described. Frozen bovine pituitaries were homogenized (2 kg) in 4l of 0.15 M $(NH_4)_2SO_4$ and centrifuged at 13,000 x *g* for 20 min. The supernatant was adjusted to pH 3.5 by the addition of 0.5 M HPO_3; the resulting precipitate was then removed by centrifugation. The supernatant was adjusted to pH 6.5 - 7.0 by the addition of 1 N NaOH; and 290 g of $(NH_4)_2SO_4$/l was added. The resulting precipitate was discarded and additional $(NH_4)_2SO_4$ (250 g/l) was added to the supernatant. A precipitate with FGF activity was formed and was then collected by centrifugation, distilled with water, dialyzed against water for 24 hr, and lyophilized. Further purification of FGF was achieved by dissolving the FGF fraction to a final concentration of 20 mg/ml in 0.1 M $NaPO_4$ (pH 6.0) and by chromatography on carboxylmethyl-Sephadex C-50 (CM-Sephadex C-50). The biologically active peak was further purified by chromatography on a series of columns: Sephadex G-75, Sephadex G-50, and CM-Sephadex C-50 (eluted with a linear NaCl gradient). The final product was considered homogeneous because it gave a single peak on Sephadex-75 and CM-Sephadex NaCl gradient elution, and it gave a single band on disc gel electrophoresis. Five milligrams of FGF were obtained per kilogram of pituitary gland. Further analyses revealed that FGF, a polypeptide rich in lysine and arginine, has a molecular weight of 13,300. FGF is a potent mitogenic factor in 3T3 fibroblasts; it was active at concentrations as low as 0.01 ng/ml, and a maximal effect was observed at 1 ng/ml.

4188 PHAGOCYTIC ACTIVITY OF LEUKAEMIC BLASTS. (Eng.) Neuwirtova, R. (Medical Faculty, Charles Univ., Prague, Czechoslovakia); Setkova, O.; Houskova, J.; Poch, T.; Dorazilova, V.; Donner, L. *Acta Haematol. (Basel)* 53(2):17-24; 1975.

4189 ISOLATION AND CHARACTERIZATION OF THE PLASMA MEMBRANE FROM YOSHIDA HEPATOMA CELLS. (Eng.) Rethy, A. (Inst. General Physiology, Univ. Ferrara, 44100 Ferrara, Italy); Trevisani, A.; Manservigi, R.; Tomasi, V. *J. Membr. Biol.* 20(1/2): 99-110; 1975.

4190 CATION PERMEABILITY AND OUABAIN-INSENSITIVE CATION FLUX IN THE EHRLICH ASCITES TUMOR CELL. (Eng.) Mills, B. (Dept. Biol., Syracuse Univ., N.Y.); Tupper, J. T. *J. Membr. Biol.* 20(1/2):75-97; 1975.

4191 STUDY OF THE MECHANISM OF K+-DEPENDENT SWELLING OF EHRLICH ASCITE CARCINOMA (EAC) CELLS. (Rus.) Polivoda, B. I. (Res. Inst. Medical Radiology, Acad. Med. Sci. U.S.S.R., Obninsk, U.S.S.R.) *Biofizika* 20(1):160-161; 1975.

4192 THE EFFECT OF ADENOSINE 3',5'-MONOPHOSPHATE ON THE CELL CYCLE OF KB CELLS [abstract]. (Eng.) Asnes, C. F. (Boston Univ. Grad. Sch., Mass.). *Diss. Abstr. Int. B* 35(9):4356; 1975.

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4194 POLYSACCHARIDES OF METAPLASTIC MUCOSA AND CARCINOMA OF THE GALLBLADDER. (Eng.) Laitio, M. (Dept. Pathological Anatomy, Univ. Turku, Finland); Terho, T. *Lab. Invest.* 32(2):183-189; 1975.

4195 ISOLATION AND CHARACTERIZATION OF PROTEOGLYCANS FROM THE SWARM RAT CHONDROSARCOMA. (Eng.) Oegema, T. R., Jr. (Dept. Oral Biol., Univ. Michigan, Ann Arbor); Hascall, V. C.; Dziewiatkowski, D. D. *J. Biol. Chem.* 250(15):6151-6159; 1975.

4196 APPARENT CELLULAR INGRESS OF ALBUMIN IN WALKER 256 TUMOR AND RAT MUSCLE. (Eng.) Jewell, W. R. (Univ. Kansas Med. Cent., Kansas City, Kans. 66103); Krishnan, E. C.; Schloerb, P. R. *Cancer Res.* 35(2):405-408; 1975.

4197 DYSPROTEINEMIA AND PARAPROTEINEMIA IN CHRONIC LYMPHOLEUKEMIA. STUDIES WITH THE AID OF DISC-ELECTROPHORESIS IN POLYACRYLAMIDE GEL. (Rus.) Pushkarev, I. A. (Riga Medical Inst., Riga, U.S.S.R.). *Probl. Gematol. Pereliv. Krovi.* 19(8): 36-41; 1974.

4198 THE GLYCOLYTIC ENZYME ACTIVITY OF THE HUMAN CERVIX UTERI. (Eng.) Pedersen, S. N. (Fibiger Lab., Copenhagen Ø, Dnemark). *Cancer* 35(2):469-474; 1975.

4199 ROLE OF ENZYME TURNOVER AND DNA REPLICATION IN REGULATING THE LEVEL OF ASPARTATE TRANSCARBAMYLASE DURING THE EUCARYOTIC CELL CYCLE. (Eng.) Wilkins, J. H. (Virginia Polytech. Inst. State Univ., Blacksburg); Schmidt, R. R. *Fed. Proc.* 34(3):651; 1975.

4200 FORMS OF CYTOSOLIC GLYCEROL-3-PHOSPHATE DEHYDROGENASE IN NORMAL AND NEOPLASTIC TISSUES. (Eng.) Rittmann, L. (Syracuse Univ., N.Y.); Ostro, M.; Kornbluth, R.; Fondy, T. *Fed. Proc.* 34(3): 676; 1975.

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4201 HEPATIC ADENOMAS AND ORAL CONTRACEPTIVES. (Eng.) Sherlock, S. (Royal Free Hosp., Pond St., London, England). *Gut* 16(9):753-756; 1975.

A progress report of the association between increased reports of hepatic adenoma and the use of oral contraceptives is presented. The various and confusing terminology assigned to the lesion is discussed, and use of the terms "adenoma" and "focal nodular hyperplasia" is considered most appropriate; hepatocellular carcinoma is not reported to date. The liver lesions are associated with most of the commonly used oral contraceptives, including combinations of norethynodrel, mestranoldiethisterone, ethyloestradiol, norgestrol, norethisterone, and ethinylestradiol. Usually occurring after at least two years use of "the pill", presenting symptoms may include constant right upper quadrant abdominal pain, an abdominal mass, or tumor rupture with hemorrhage into the peritoneal cavity. Use of hepatic arteriography is described and considered the best diagnostic aid prior to rupture. The liver size seems unrelated to the possibility of rupture, and the prognosis after tumor resection is good. Hepatic adenoma is also reported in postmenopausal women receiving hormone replacement, and slow growing primary liver cancer is found in men receiving androgen therapy. The role of the oestrogen or the progesterone component in causing the hepatic lesion is uncertain, as is the oncogenic mechanism; a direct effect and an indirect action *via* enzyme induction are both considered. The independent development of vascular changes in women using oral contraceptives is also discussed. The full extent of the problem is unknown; over five million women in the U.S. have taken oral contraceptives, and a small but increasing number of hepatic adenomas in young women are reported. While regular abdomen examination is not thought necessary, the possibility of hepatic adenoma must be considered in women taking oral contraceptives or hormone replacements. (19 references)

4202 STEROIDS AND HUMAN BREAST CANCER. (Eng.) McGuire, W. L. (Univ. Texas Health Science Center, San Antonio, Tex. 78284); Chamness, G. C.; Costlow, M. E.; Richert, N. J. *J. Steroid Biochem.* 6(5):723-728; 1975.

Studies of specific estrogen receptors and of the mechanisms of action of the receptor-estrogen complex in human mammary tumors, induced rat mammary tumors, and other estrogen target tissues are reviewed. Estrogen has been shown to act directly on the normal mammary gland to promote growth and differentiation, and to also stimulate the release of pituitary prolactin. However, experiments showing prolactin stimulation of tumor growth in the absence of ovarian steroids, albeit of brief duration, have suggested only a secondary role of estrogen. Studies of the nuclear binding of estrogen receptors have demonstrated the presence of estrogen receptors in the cytoplasm of dimethylbenz(a)anthracene-induced hormone-dependent rat mammary tumors, and the accumulation of injected estrogen in their cell nuclei *in vivo*, apparently still bound to a 4-5S form of the receptor. Experiments employing the R3230AC transplantable mammary carcinoma have indicated that the chromatin of the autonomous breast tumor cells possesses the capacity for extensive receptor-estrogen interaction. Cytoplasmic receptor-estrogen also binds equally well to nuclei prepared from target and nontarget tissues, in a manner strictly proportional to the available receptor-estrogen. The quantitation of estrogen receptor in human breast cancer specimens is described. Receptors in 154 primary tumors and 72 metastatic tumors have been assayed. The estrogen receptor values in primary tumors range from zero to almost 1,000 femtoM/mg of cytosol protein. Data from 436 treatment trials in 380 patients are also reviewed, and clinical correlations are presented. Thirty-three percent of 211 ablative therapy treatment trials yielded objective tumor regression; 8% of 94 trials in patients with negative tumor receptor values were successful, while 55% of 107 trials in patients with positive tumor receptor values succeeded. Of 170 additive therapy trials, 8% of 82 trials in patients with negative tumor receptor values succeeded, compared to 60% of 85 trials in patients with positive tumor receptor values. In addition, 27% of 55 trials yielded responses to a variety of endocrine therapies, including antiestrogens and aminoglutethimide. Thus the data reveal that estrogen receptor assays can be helpful in predicting the results of endocrine therapy for metastatic breast cancer. (32 references)

4203 VINYL CHLORIDE AND PUBLIC HEALTH. (Eng.) Anonymous. *Med. J. Aust.* 1(15):455-456; 1975.

Current knowledge about occupational and consumer exposure to vinyl chloride (VC) is reviewed. The manufacture of polyvinyl chloride (PVC) is described; the reaction of chlorine and ethylene, the suspension method, the addition of modifying agents, and the exothermic polymerization is noted. The possibility of transcutaneous absorption to worker's hands is acknowledged, as industrial atmospheric VC concentrations of 600-1,000 ppm are found. The characteristic clinical picture occurring in workers chronically exposed to the gas is entitled "vinylchloride-krankheit": symptoms may include sclerotic changes in the skin of the hands, cold sensitivity, Raynaud's phenomenon, and band-like osteolysis of the terminal phalanges. In addition, thrombocytopenia and splenomegaly are frequently found, and pulmonary fibrosis, restrictive ventilation, and diffusion defects also occur. However, greatest concern and publicity arises from the discovery of angiosarcoma of the liver in five VC workers. The association of VC with the otherwise rare angiosarcoma is highly suspicious, and the carcinogenic effect of VC is demonstrated in animals. However, the translation of such experimental findings to man must consider species differences, the possibility of co-carcinogens, and differing latent intervals. The present upper limits of VC exposure

in the U.K. are set at 200 ppm, while a limit of 50 ppm is recommended in the U.S. In addition, the limit of VC monomer is 10 ppm for rigid PVC containers and one ppm for flexible PVC films in contact with foods, while one part per 10 million is allowed in foods packaged in PVC containers. The newly acquired intolerance to pollution and the conflicting employer *vs* employee forces, are discussed. However, it is stated that the potential dangers of VC relate to the worker with the basic material, and not to the user of the finished product. (9 references)

4204 VINYL CHLORIDE: ITS SAFETY HAZARDS. (Dut.) Zielhuis, R. L. (No affiliation given). *Ned. Tijdschr. Geneeskd.* 119(2):63-66; 1975.

Recent literature on the carcinogenicity of vinyl chloride (VC), an intermediary in PVC production, is reviewed. Angiosarcoma of the liver, a rare tumor, was found in workers exposed to VC during production and processing in the USA, Great Britain, Sweden, and West Germany. A retrospective survey revealed increasing incidence of tumors of the digestive and respiratory tracts and of lymphomas with increasing intensity and duration of occupational VC exposure among 7,000 workers. Skin and lung carcinomas were found in rats exposed to 30,000 ppm VC. Malignant tumors were found in rats, hamsters and mice exposed to 50-10,000 ppm VC for 12 mo to 130 wk. The discovery of the carcinogenic properties of VC has resulted in a drastic lowering of the maximum allowable conc. of VC in workplace air from 200-500 ppm to 50-25 ppm and even to as low as 1 ppm in manufacturing plants in the USA. (15 references)

4205 RESEARCH FINDS AROMATIC AMINES EXPOSURE CAUSE OF INCREASED NUMBER OF TUMORS. (Eng.) Orjelick, R. (Div. Occupational Health and Radiation Control, Health Commission of New South Wales, Australia). *Int. J. Occup. Health Saf.* 44(5): 46-47; 1975.

The relationship of occupational exposure to aromatic amines and an increased incidence of urinary tract tumors is reviewed. A statistically significant association between exposure and subsequent tumor development has been found for 4-aminodiphenyl, benzidine, 6-naphthylamine, and 2-naphthylamine; a strong association is suspected for 2-acetylaminofluorene, 3,3'-dichlorobenzidine, 4'-dimethylaminoazobenzene, N'nitrosodimethylamine, diphenylamine, O-tolidine, O-dianisidine, α-naphthylamine thiourea, auramine, and magenta. Human absorption occurs *via* inhalation of the dust or vapor, absorption through intact skin, and by ingestion; individual hygiene is considered a most important factor. The proportion of bladder tumors estimated to be related to industrial carcinogen exposure varies from 1 to 33%. Occupations considered to have a definite causative association with bladder cancer include rubber and cable work, patent fuel, gas, and pitch work, laboratory work, color and dye work, rodent extermination, chemical work, and paint and pigment manufacture. Occupations assigned a statistical association with bladder cancer include leather work, stokers, hairdressing, tailoring, coal mining, printing, electrical work, and kitchen work. Such factors are tabulated and individual evidence is cited. (9 references)

4206 CHLORINATION: THE CURRENT DILEMMA. (Eng.) Rehberger, G. W. (CH2M Hill, Inc., Reston, Va.). *Water & Sewage Works* 122(11): 62-65; 1975.

Implied relationships between organics in the drinking water, chlorination, chlorinated waste discharge industrial waste discharges, and elevated levels of cancer in several areas of the nation are reviewed. Literature on the chlorination of organic materials is mainly related to the problems of taste, odor, detection, and identification. No valid relationship between the fate of organic pesticides and chlorinated organic materials suspected to be carcinogenic has been developed. A statistical analysi attempts to show a relationship between the incidenc of cancer and use of drinking water from the lower Mississippi River; however, no positive statistical relationship between cancer incidence and usage of water containing organic chemical compounds has been found. Another report revealed a higher concentration of chloroform and other trihalogenated methanes in chlorinated surface and ground water supplies. A further report has indicated that successive applications of chlorine to water removed from polluted rain water sources increases the concentration of chlorinated hydrocarbons through the treatment process train. Numerous chlorinated hydrocarbon compounds in the chlorinated effluent from both primary and secondary sewage treatment plants, not present in the raw sewage, are also elsewhere identified. Use of activated carbon as a filtration media, and an end to the widespread use of chlorine as a water disinfectant, is suggested to significantly reduce the halogenated organics in drinking water. However, such alternate treatment processes may create new problems. In general, no conclusive or strong circumstantial evidence exists that chlorinated drinking water and cancer can be positively linked; however, some weak circumstantial evidence does exist. (9 references)

4207 WHAT WE HAVE LEARNED ABOUT PLUTONIUM FROM HUMAN DATA. (Eng.) Voelz, G. L. (Los Alamos Scientific Lab., Los Alamos, N. M. 87544). *Health Phys.* 29(4):551-561; 1975.

Human data on plutonium deposition, internal distribution, and excretion, as obtained by observations after accidental occupational exposure, long-term followup studies on plutonium workers, and autopsy tissue analyses are reviewed. Accidental exposures through inhalation or wounds are studied

for absorption rates of plutonium, urinary excretion values, and evaluation of possible treatment techniques. No cases of acute human pathology following plutonium exposure are yet reported, while the only chronic findings are the formation of fibrous nodules around the site of plutonium depositions in wounds in eight persons. Followup studies of 26 highly-exposed plutonium workers have revealed exposures of around the current permissible body burden for nearly 30 yr. Their medical studies note no abnormal ailments and no significant lung or bone abnormalities; sputum cytology shows no neoplastic changes, and chromosome analysis of peripheral lymphocytes reveals no abnormalities. While early reports on 41 autopsies show no undue accumulation of plutonium in workers, selected tissues from 370 later autopsies confirm the increased plutonium in these workers with higher exposure potential and show considerable individual variations in distribution. Such variations appear related to the conditions of plutonium exposure, including mode of exposure, particle size, chemical composition, solubility in serum or tissue fluids, and time of internal redistribution. Highest concentrations are consistently found in the tracheobronchial lymph nodes, followed by lungs, liver, and bone. Methods used to estimate body burdens by urinary excretion appear to be generally conservative, as compared to autopsy tissue burdens. (25 references)

4208 A SURVEY OF THE BENEFITS AND RISKS IN THE PRACTICE OF RADIOLOGY. (Eng.) Payne, J. T. (Dept. of Radiology, Univ. of Minnesota, Minneapolis, Minn.); Loken, M. K. *CRC Crit. Rev. Clin. Radiol. Nucl. Med.* 6(3):425-437; 1975.

Benefits and risks in the practice of radiology are reviewed. The diagnostic value of radiology is not questioned in most medical circles. The radiation doses per exam are now relatively low. The risk-benefit facts on irradiation are based on low level, fractionated doses spread over a life time. The somatic effect of primary concern is the irradiation of red bone marrow and the induction of leukemia. As of the present, no statistically significant figures have linked cancer and dose-effect relationships at low-dose levels of irradiation. A theoretical fitted straight line estimates that the risk of leukemia is one or two cases per rad per year for one million persons irradiated. Yet, risk for leukemia and other cancers appears to be 40% higher for children irradiated *in utero*. The irradiation of the fetus *in utero* may lead to somatic effects such as impairment of growth, microcephaly, and mental retardation. Genetic effects of irradiation are more difficult to detect than somatic ones. Predicting the genetic consequences to man from radiation exposure involves the use of many assumptions, not all of which can be experimentally validated. At present there are few coordinated attempts to determine whether a diagnostic radiation procedure has been of clinical value in each or any given number of cases. Furthermore there is no impartial method for determining that a given examination is truly indicated. (no references)

4209 THE EFFECTS OF DIAGNOSTIC X-RAY EXPOSURE ON THE HUMAN FETUS: AN EXAMINATION OF THE EVIDENCE. (Eng.) Oppenheim, B. E. (Dept. Radiology, Univ. Chicago, 950 E. 59th St., Chicago, Ill. 60637); Griem, M. L.; Meier, P. *Radiology* 114(3):529-534; 1975.

The effects of diagnostic x-ray exposure on the human fetus are reviewed. Prenatal irradiation and the gross death rate reveals that among 6000 caucasian and 9000 black children exposed *in utero* to diagnostic x-rays, the death rate is multiplied by two for the white children and does not change for the black children. Another report shows that the rate of prenatal exposure to x-rays is about 50% higher for children with malignancies than for the controls, corresponding to a relative risk of malignancy following prenatal irradiation of 1.6. A statistically significant alteration of the sex ratio is found for offspring of black women who themselves have been exposed *in utero* to diagnostic x-rays before 30 wk of fetal life. The relation between preconception irradiation and leukemia with regard only to maternal exposure reveals the risk to be between 1.55 and 1.73. Preconception irradiation is also linked to mongolism. Each of these studies is subject to criticism and for each study proving one point there are one or more studies proving the exact reverse. Comparisons with studies in which radiation exposure occurred on a nonselective basis demonstrate a significant discrepancy in each instance. This casts some doubt on the validity of all these studies, and suggests that exposure to diagnostic x-rays may be less harmful than is sometimes claimed. (51 references)

4210 MALIGNANT NEOPLASMS IN CHILDREN. (Rus.) Durnov, L. A. (Inst. Experimental and Clinical Oncology, Moscow, USSR); Kiselev, A. V. *Pediatriia* (6):85-89; 1975.

Epidemiological, clinical and therapeutic aspects of malignant tumors in childhood are reviewed. Burkitt's tumor is believed to be of viral etiology. Recently, cats and dogs are suspected to be the primary hosts of oncogenic viruses causing leukemia in humans. Metastases of malignant tumors into the placenta and fetus were observed in 24 cases during the 1866-1966 period. These cases include melanoma as the primary tumor in 11 cases, breast cancer in four cases, cancer of the lungs and stomach in two cases each, and lymphosarcoma, sarcoma of the hip, of the ethmoid bone, adrenal gland and ovary in one case each. The increased tumor morbidity among children irradiated during their intrauterine lives indicates that irradiation is a risk factor in genetically predisposed children. Irradiation is most hazardous during the first three months of intrauterine life. Inborn developmental defects and neuroblastoma are suspected to have a common etiology. The familial cancer syndrome is believed to be due to an interaction of genetic and exogenous (viral) factors. (46 references)

4211 STATISTICAL REVIEW OF CANCER IN ENGLAND AND WALES. (Eng.) Anonymous. *Br. Med. J.* 4(5991):245-246; 1975.

The most recent survey of the voluntary cancer registration scheme in England and Wales is discussed. While noted to have potential epidemiological significance, the inconsistent reporting and level of inaccuracy is suggested to mask the subtle clues emerging from time-and-space cluster analysis. Cancer rates of 332.2 and 300.7/100,000 are reported for males and females, respectively. Lung cancer accounts for 29% of all cancer in men, while breast cancer is responsible for 24% of all cancers reported in women. The registration of gastric cancer is falling slowly, but not as fast as the decline in mortality might suggest, while the rates of other alimentary tract tumors are increasing. There is also an apparent rise of Hodgkin's disease and myeloma cases. However, registrations of borderline conditions, such as myelofibrosis and polycythemia, are assumed to indicate gross underestimates of their frequency. There is also considerable variation in the apparent incidences of carcinoma in situ of the cervix; regional reports range from 1.1 to 15.9 per 100,000. Cancers of the lip, salivary gland, larynx, uterus, testis, and eye have five year-age corrected survival rates above 50%, while tumors of the large bowel, breast, prostate, and bladder, and the lymphomas have corrected five year survival rates of 25-50%. Although the five-year survival is considered good reason to assume cure for some cancers, cancers of the breast, head and neck, cervix, prostate, and the lymphomas may account for deaths up to 15 yr after initial treatment. No conclusions on the effectiveness of new types of treatment can yet be made, but the accurate recording of cases is stressed. (1 reference)

4212 DIFFERENCES IN SURFACE MEMBRANE COMPONENTS BETWEEN NORMAL, VIRAL-TRANSFORMED AND REVERTANT CELLS. (Eng.) Black, P. H. (Massachusetts General Hosp., Boston, Mass.); Chou, I. N.; Roblin, R. *Proc. Int. Cancer Congr. 11th.* Vol. 1 *(Cell Biology and Tumor Immunology)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 119-129.

Experiments investigating intracellular and extracellular membrane stabilization mechanisms are reviewed, and changes found in the plasma membrane of transformed cells are described. Electron microscopic examination of thin sections of untransformed 3T3 mouse cells, simian virus 40 (SV40)-transformed mouse cells (SV-3T3), and revertant cells (Rev SV-3T3) has revealed a population of 70 A alpha filaments in the peripheral cytoplasm of confluent 3T3 and revertant cells. Abundant alpha filaments are correlated with the presence of contact inhibition of growth. While the precise mechanism is unknown, the data suggest a role in modulating cytoplasmic viscosity and in motility control of the cell. An interaction of the filament with the plasma membrane acting to rigidify the plasma membrane is also suggested, as is the involvement of the microtubule system in the movement of concanavalin A (Con A) binding sites. Studies on the stabilization of the plasma membrane by substances outside the cell have noted the role of the sulfonated acid mucopolysaccharides (SAMPS). Examination of the production, distribution, and turnover of SAMPS in untransformed 3T3 cells, SV3T3 cells, and Con A-selected revertants has revealed qualitative changes and a 2-5-fold decrease in the amount of cell-associated SAMPS in transformed cells; reversion of the transformed phenotype results in a reversion of the SAMPS synthetic capacity as well as the nature of the species synthesized. Radioactivity studies of the localization of SAMPS have revealed that 70-85% are located at the cell periphery and have indicated a correlation between high levels of SAMPS synthesis and low saturation density (increased cellular adhesiveness) in cell cultures. Data also suggest that enhanced cellular adhesiveness may result in a diminution of lateral movement of plasma membrane components. Changes in trilaminar membrane constituents are discussed, and changes in glycolipid patterns are noted. The absence of a large molecular weight glycoprotein is noted in DNA and RNA-virus-transformed cells; protease exposure may also affect the plasma membrane. It is uncertain whether intracellular, extracellular, or intramembranous factors are responsible for increased membrane fluidity; their interrelationship is suggested. (69 references)

4213 HERPES VIRUS AND HUMAN CANCER. *(Eng.)* Munk, K. (Institut fur Virusforschung am Krebsforschungszentrum, 69 Heidelberg, West Germany) *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 288-290.

The relationship between herpes simplex virus (HSV) and human cancer is reviewed. The biological and antigenic properties of the HSV types are correlated with the sites of the lesions from which they are recovered; HSV-2 is predominantly isolated from genital sites and HSV-1 from lips and skin lesions. After the initial infection, HSV persists permanently in a latent stage in the organism, the nonproductive virus-host relationship exhibited by this virus being known to be one of the essential prerequisites for the expression of the oncogenic functions of DNA viruses. The data from seroepidemiological investigations support an association between HSV-2 and cervical cancer, but they do not prove that HSV plays a role in the etiology of the disease. Laboratory investigations using immunofluorescence, molecular nucleic acid hybridization, and antigenic methods supported the oncogenic potential of HSV. However, tumor induction experiments in laboratory animals did not support the presumed oncogenicity of HSV; better evidence for the oncogenic potential of the virus emerged from attempts to transform cells with HSV in culture. In these *in vitro* systems, HSV exhibited oncogenic properties. The conclusion at the present time that HSV should be seriously considered as a virus with oncogenic properties is

supported by the fact that other viruses of the herpes group (e.g., Marek's disease virus and some simian herpes viruses) are oncogenic in their natural or experimental hosts, and the fact that there is good evidence that the Epstein-Barr virus is oncogenic in man. (32 references)

4214 IMMUNOLOGICAL BASIS FOR LATENCY, RECURRENCES, AND PUTATIVE ONCOGENICITY OF HERPES SIMPLEX VIRUS. (Eng.) Lehner, T. (Guy's Hosp. Medical and Dental Sch., London SE1 9RT, England); Wilton, J. M. A.; Shillitoe, E. J. *Lancet* 2(7924): 60-62; 1975.

The relation between primary infection, latency, and recurrent infection by herpes simplex virus (HSV) has been the subject of many virological, immunological, histochemical, and clinical investigations. The development of latency and recurrent infection after primary HSV infection can be interpreted in terms of cell-mediated and antibody responses to virus-specific antigens and Fc receptors on the surface of the infected cells. Primary infection induces immune responses to the virus, and antibody and cell-dependent cytotoxic mechanisms kill most of the virus and virus-infected cells accessible to killer cells. HSV is sequestrated to the nerves and migrates centripetally along the axons to the trigeminal or sensory ganglia. Latency in the trigeminal ganglion may be mediated by IgG antibodies binding to both HSV antigens and Fc receptors. Derepression of the viral genome may be induced by factors that weaken the binding of antibodies to the antigen and Fc receptor; the virus replicates and migrates centrifugally along the axon, to be shed at the nerve endings. In the presence of some defect in T lymphocytes, acting at the neuroepithelial junction, a recurrent herpetic lesion is precipitated. There is some evidence that HSV may be associated with squamous-cell carcinoma, and it is postulated that the enhanced cell-mediated and antibody responses to HSV may destroy cells containing the viral genome but allow the emergence of an oncogenic genome. Double binding of the Fc receptor and HSV antigen by IgG antibodies or immune complexes on the surface of carcinoma cells may prevent killing and allow these cells to proliferate into invasive tumors. (55 references)

4215 TRANSFER FACTOR IN VIRAL INFECTIONS. (Eng.) Zuckerman, A. J. (No affiliation given). *Nature* 258(5530):14-16; 1975.

The nature and action of transfer factor is reviewed, and its effectiveness in numerous viral infections, including hepatitis B infections, is discussed. Transfer factor is described as a dialyzable leukocyte extract that initiates and augments delayed-type hypersensitivity and cell-mediated immunity in normal persons. Although initially considered to be an antigen-specific polypeptide-polynucleotide molecule, later studies demonstrate an active fraction with the properties of a short polypeptide chain joined to RNA bases in a ratio of 2:1. Transfer factor is considered a soluble indicator of cellular immunity, capable of inducing nonsensitized lymphocytes to produce lymphokines. Clinically, transfer factor activates uncommitted and nonsensitized recipient lymphocytes, confers specific skin sensitivity, is exceedingly potent, but does not transfer the capacity for antibody formation. Transfer factor is clinically used to correct certain primary immunodeficiency states; favorable responses are reported in patients with generalized vaccinia, herpes zoster, neonatal herpes virus infections, measles, "giant-cell" pneumonia, subacute scloerosing panencephalitis, veruca vulgaris, plus numerous other infectious diseases. However, despite previous reports, a randomized double-blind study of 30 patients failed to confirm a casual relationship between therapy with transfer factor and wart regression. Much attention is directed to the treatment of hepatitis B virus infection with transfer factor; temporary falls in the levels of hepatitis B antigen are reported after the use of transfer factor in patients with antigen-positive chronic active hepatitis. Administration of "specific" transfer factor prepared from subjects recently recovered from hepatitis B infection increases the number of T lymphocytes and suggests stimulation of cell-mediated immunity, while treatment with lymphocytes of a recovered patient results in liver function tests implying liver damage. While generally therapeutically effective, the risk of transfer factor exciting generalized hypersensitivity reactions to dessimated microbial or other antigens is also recognized. (no references)

4216 A SPECULATIVE COMPARISON OF ALLOTYPIC SUPPRESSION AND ALLOTYPIC BLAST TRANSFORMATION: CONTROL OF EXPRESSION OF T AND B CELL IMMUNOGLOBULIN ALLOTYPIC MARKERS BY A B CELL PRODUCT. (Eng.) Sell, S. (Univ. California, San Diego, Medical Sch., La Jolla, Calif. 92037). *Transplant. Rev.* 27:135-156; 1975.

A comparison of the similarities and differences between allotype suppression and allotype transformation is presented; special attention is given to the control of expression of T and B cell allotypes of rabbit immunoglobulin (Ig) molecules. Eight shared characteristics of allotype suppression and allotype transformation are described, while it is noted that only rabbit allotypic sera will produce suppression. A discussion of allelic expression of lymphoid cells notes demonstrations of allelic exclusion and concludes that the Ig-bearing cells upon which antiallotypic sera act have the capacity to express and synthesize the products of both Ig alleles. The phenomenon of mixed allotypic sequential stimulation is discussed, the restimulation of blocked lymphocyte cultures is described, and antiallotypic sequential stimulation experiments are diagramatically summarized. Studies on the expression of lymphocyte surface allotypic markers are correlated with events occurring during blast transformation, and the mixed allotype sequential stimulation and endocytosis findings are compared to the *in vitro* allotype suppression reversal. In view of data supporting allelic in-

clusion in heterozygous lymphoid cells reactive to antiallotypic sera, and the lack of evidence for T-cell mediated suppression in the rabbit, a direct cell model for allotypic suppression based on double allelic expression is proposed. The B-cell product suppression of T and B-cell allotypic markers is noted, and the single cell model for allotypic suppression is symbolically diagramed. It is postulated that antiallotype antibody induces suppression of expression of that allotypic marker in uncommitted T and B cells. Committment to a given allotype is suggested to occur only in differentiated cells, reversibility is allowed to less differentiated T and/or B cells; allotypic suppression thus represents control of T and B-cell expression by a B-cell product. (108 references)

4217 REDUCED INCIDENCE OF SPONTANEOUS TUMORS: ANOTHER STATISTICAL ANALYSIS. (Eng.)
Casagrande, J. (Sch. Medicine, Univ. Southern California, Los Angeles, Calif. 90033); Pike, M. C. *Science* 190(4216):808-809; 1975.

Another statistical analysis is given to previously reported data on reduced spontaneous mammary tumor incidence in C3H/He mice treated with polyadenylate-polyuridylate. The recalculation, correcting for the intercurrent deaths, revealed a 49% rate of mammary tumors in controls and a 44% tumor rate for treated animals, a statistically insignificant difference. The proper statistical methodology requires knowledge of the actual times of intercurrent deaths and times of diagnosis of mammary tumors. The tentative conclusion is that such treatment prevents tumors in a proportion of animals, but fails to delay the appearance of the tumor in those mice it fails to protect completely. (3 references)

4218 THE RESPONSE TO PHOSPHORYLCHOLINE: DISSECTING AN IMMUNE RESPONSE. (Eng.) Kohler, H. (La Rabida Inst. and Dept. Pathology and Biochemistry, Univ. Chicago, Chicago, Ill. 60649). *Transplant. Rev.* 27:24-56; 1975.

Studies on the antibody response to phosphorylcholine (PC), as characterized by restrictions in the epitope specificity, idiotype composition, immunoglobulin (Ig) class, and involvement of cell types, are presented and discussed. The inhibition of PC-specific plaques elicited in BALB/c mice is noted; the similarity between PC myeloma proteins and anti-PC antibodies is investigated by comparing their affinity constants in equilibrium dialysis, the fingerprints of their light chains, and their banding profiles in isoelectric focusing. The antibodies to PC in BALB/c mice are thus determined to be of oligoclonal origin. Additional studies note that anti-idiotypic antibodies are antireceptor antibodies. The presence of TEPC-15 idiotype on the surface of immunocompetent cells for PC is demonstrated by morphological, biochemical, and functional assays, while other experiments have isolated and characterized the receptor Ig for PC with biochemical methods; specific suppression by heterologous and anti-idiotypic sera has been shown. Two different experimental protocols by which the specific suppression of the PC response in mice is observed are cited. The experimental evidence indicates that adult suppression is due to reversible blockade of receptor by ARA and that neonatal suppression is the result of clonal depletion. Further studies on adult and neonatal suppression of the response to PC by ARA provide evidence that an antibody can control the synthesis of a specific antibody. It is also found that immunization with antigen induces ARA; speculations on the biological significance of the autoantibody which is idiotype-specific for the induced anti-PC antibody suggest a suppressed response to PC. Four kinds of supportive findings are cited: (1) responses to PC of repeatedly immunized BALB/c mice and the responses to PC of A-mice immunized with TEPC-15, (2) the PC response of cultured spleen cells from normal and immunized BALB/c mice, (3) the response to PC and TEPC-15 of BALB/c mice immunized with C-polysaccharide, and (4) the primary *in vitro* PFC response to PC and homologous red blood cells. A hypothesis on the function of anti-ARA in the regulation of immune reactions proposes a two cell-two way model of regulation; schematic representations of the entire response repertoire of the immune system and of the possible interactions of antibodies and antigens of a response unit are presented. It is concluded that ARA can determine the expression of variable genes early in ontogeny and control the level of expression in adult animals. (68 references)

4219 EPIDERMODYSPLASIA VERRUCIFORMIS: A RETROSPECTIVE GLANCE AND CURRENT APPRAISAL. (Eng.) Waisman, M. (220 Madison St., Tampa, Fla. 33602). *Cutis* 16(4):627-632; 1975.

The development of the recognition of *epidermodysplasia verruciformis* (EV) as a distinct disease is reviewed. Clinical and microscopic characteristics of EV are described, and a recent case study is presented. Initial inoculation experiments, followed by numerous and varied auto- and heteroinoculations have indicated that personal and familial occurrence depends upon some then unknown and special predisposition. Infectiousness is relative, and the spectrum of resistance is broad and unpredictable. Observations note fluctuating susceptibility, apparent spontaneous remissions, and the relocation of the lesions. Ultrastructural studies reveal viral particles forming crystalloid structures in certain nuclei of the upper rete. However, the virus is not found in all typical cases of EV. Autoradiography shows that lesions of EV incorporate much tritiated thymidine in both the basal and intermediate level cells, those cells are thus suggested to be the DNA-synthesizing cells. However, tritiated uridine incorporation is retarded and diminished not only in the large pale dysplasia granular cells of EV, but also in the apparently normal basal cells. In evaluating the mechanism of the virus replication and disease spread, it is suggested that normal subjects restrain the oncogenic proclivity of the defective virus, while susceptibles breed clones of malignant

ells. A case is reported of a 39-yr-old woman, resenting large varicose planae abundantly spread ver her legs and forearms, and a plantar verrucae n her heel. A family history of extensive verucae was noted. A biopsy specimen showed vacuolar hanges in the upper rete characteristics of veruca plana. Local treatment of the plantar verruae was ineffective, as were intramuscular injeions of an autogenous vaccine prepared from a lantar lesion. Whereas no clinical evidence to upport the supposition of depressed humoral or ell-mediated immunity in EV is presented, it is ypothesized that patients affected suffer a owered epidermal immunity directed selectively oward the wart-tissue. (29 references)

220 CLINICAL APPLICATIONS OF BONE-MARROW CULTURE. (Eng.) Goldman, J. M. Hammersmith Hosp., London W12 OHS, England); Sultan, . *Lancet* 2(7937):696-698; 1975.

he use of *in vitro* culture methods for studying uman hemopoietic cells has advanced greatly since 970. These methods have contributed to the understanding of the mechanisms controlling granulopoisis, though the physiological role of colony stimuating factor needs further clarification. In eukemia they offer an approach to the study of ossible causal factors and to the characterization f leukemic cell defects. Results already obtained upport the concept that the bone-marrow in acute yeloid leukemia consists of coexisting populations f normal and leukemic cells, with a leukemic clone redominating in relapse and normal clones regenerting in remission. For the individual patient, *n vitro* methods may prove useful in assessing rognosis and in confirming the completeness of emission; the detection of early relapse may then ndicate the need for changing or reinstituting herapy. Further studies may aid the classification f the "preleukemic" states and may help in the dentification of the various causes of neutropenia. 17 references)

221 GENETICS OF DIFFERENTIATION. (Eng.) Ohno, S. (City Hope Natl. Medical Center, uarte, Calif. 91010). *Proc. Int. Cancer Congr. 1th.* Vol. 1 *(Cell Biology and Tumor Immunology).* lorence, Italy, October 20-26, 1974. Edited by ucalossi, P.; Veronesi, U.; Cascinelli, N. New ork, American Elsevier, 1975, pp. 69-71.

tudies on the genetic control of sexual differeniation in mice are summarized. A series of embryoogical studies showed that both XX and XY mammalian mbryos have the inherent tendency to manifest the emale phenotype and that the male phenotype develops nly when embryos are continuously exposed to cirulating testosterone and/or its effective metabltes. Concordance between chromosomal, gonadal, nd phenotypic sex is assured because only the estis is capable of synthesizing an effective amount f androgenic steroids. Although steroid hormones eadily penetrate cell membranes and hence require o membrane-bound receptors, a nuclear-cytosol steroid hormone receptor protein moves into the nucleus, associates with the chromatin, and affects a regulatory gene locus. Assuming only one such locus, femaleness represents the constitutive or noninduced state, while an XY male carrying such a mutant locus is the noninducible, e.g. the testicular feminization (Tfm) mutation. Studies on affected Tfm/Y mice have shown that every conceivable androgen-target organ of mutants becomes totally nonresponsive to even massive doses of effective androgens. Consequently, most androgen target organs are missing altogether in Tfm/Y mutants; in the few remaining target organs, androgen-nonresponsiveness is correlated with virtual absence of the high affinity nuclear-cytosol androgen-receptor protein. It is concluded that the Tfm locus regulates the entire process of mammalian sexual differentiation by specifying the high affinity nuclear-cytosol androgen-receptor protein. It is further hypothesized that mammalian sex determination and differentiation may be under the control of merely two regulatory genes, both residing on the sex chromosomes. (9 references)

4222 MALIGNANT LYMPHOMA. (Eng.) Stuart, A. E. (Dept. Pathology, Univ. Edinburgh, Edinburgh, Scotland). *J. R. Coll. Surg. Edinb.* 20(5): 332-347; 1975.

The presentation, treatment, and pathology of malignant lymphoma are described; special attention is given to Hodgkin's disease. Following a brief outline of lymphoma group-treatment of patients, a description of the clinical and pathological staging of Hodgkin's disease is presented. Four clinical stages, noting the features of the original biopsy, history and physical examination, laboratory studies, and all radiographic procedures, are described. Pathological staging is determined *via* involvement found at laparotomy or by any tissue removal; procedures of the staging laparotomy are described. The Lukes histological classification of Hodgkin's disease is advocated, and consists of the following groups: (1) diffuse lesions, (2) nodular lesions, (3) nodular sclerosis, (4) mixed cellularity, (5) diffuse fibrosis, and (6) reticular type. The simpler Rye classification is also noted. The predictable spread and stability of Hodgkin's disease is discussed; nodular sclerosis is found the most stable, while lymphocyte predominance is the least stable. The diverse classifications and interpretations of non-Hodgkin's lymphoma are acknowledged and evaluated; the Rappaport classification is supported. Factors affecting the prognosis in non-Hodgkin lymphoma are discussed; survival is related to the histology. Positive bone marrow biopsies are often associated with splenic involvement; an association is also found between involved cervical or supraclavicular nodes and upper para-aortic lymphadenopathy. The histology and epidemiology and Burkitt's lymphoma, mediastinal lymphoma, angioblastic-immunoblastic lymphadenopathy, and extra-nodal lymphoma - including the thyroid, primary gastric, and mammary lymphomas - are also discussed. Conditions confused with malignant lymphoma are described, and novel cell receptor studies are summarized. (21 references)

4223 CERVICAL DYSPLASIA -- DIAGNOSIS, PROGNOSIS, AND MANAGEMENT. (Eng.) Sedlis, A. (No affiliation given). *Prog. Gynecol.* 6:559-581; 1975.

The diagnosis, prognosis, and management of cervical dysplasia is reviewed, and the role of dysplasia as a cancer precursor is investigated. Microscopic features distinguishing dysplasia from the normal epithelium include inhibited maturation, increased proliferation, pleomorphism, and variable positions of epithelial cells. The degree of neoplastic transformation of epithelium varies with different forms of dysplasia; based on the percentage of cells undergoing neoplastic transformation, dysplasia is classified as mild, moderate, or severe. Conditions found to simulate dysplasia include epithelial atypia, tissue repair, inflammation, and condylomata acuminata or papillomata. Histological diagnosis of dysplasia *via* conization, random punch biopsies, colposcopy, and colpomicroscopy is discussed. Various cytological features are noted; the differences between the various degrees of dysplasia are also reflected in the desquamated cells. Indirect statistical data supporting the concept of the premalignant potential of dysplasia reveal that dysplasia usually preceeds carcinoma *in situ*, that prevalence and incidence of dysplasia become smaller in successive age groups, and that the majority of cervical cancer cases originate in patients with dysplasia. Indirect evidence for the neoplastic character of dysplasia is also obtained from results of tissue culture, electron microscopy studies, and microspectrophotometric determination of nuclear DNA contents. While prospective studies provide various figures for progression and regression, a statistical model indicates all forms of dysplasia show progression eventually culminating in carcinoma unless the lesion is treated or disturbed by biopsy. Factors influencing the management of dysplasia, and the objectives of treatment are discussed. Treatment depends on the histological grade, patient's age, and desire for reproduction, and may involve hysterectomy, cryosurgery, or electrocauterization. It is noted that the recognition and treatment of dysplasia is a significant achievement in the control of cervical cancer. (22 references)

4224 CHROMOSOMAL LOCALIZATION OF ENZYME INFORMATION IN MAN. (Eng.) Khan, P. M. (Dept. Human Genetics, State Univ. Leiden, Wassenaarseweg 62, Leiden, Netherlands); Bootsma, D. *Proc. Int. Cancer Congr. 11th.* Vol. 1 *(Cell Biology and Tumor Immunology).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 56-63.

Current knowledge on the gene map of man, with particular reference to the loci involved in the production of enzymes, is presented. Cell fusion techniques are useful in showing that the loss of certain chromosomes from hybrids between malignant and other malignant or nonmalignant cells does influence the tumorigenic capability of the cell hybrid; somatic cell hybrids have demonstrated the occurrence of a specific integration site for the viral genome in the host DNA. Enzyme loci firmly or tentatively assigned to human chromosomes are tabulated and discussed. More than 90 loci are assigned to the X-chromosome of man, but no enzyme locus is satisfactorily ascribed to the human Y-chromosome; 1018 autosomal loci have been catalogue The A1 chromosome is the most crowded with assignments; 11 structural loci, for various enzymes, are illustrated. Use of cell hybrids has demonstrated regions carrying phosphogluconate dehydrogenase, phosphopyruvate hydratase, phosphoglucomutase, UDP-glucose pyrophosphorylase, and others. Annealing experiments have demonstrated that most of the 5s-RNA is produced at loci in the q41-42 region. Studies have indicated that chromosome 6 contains loci for phosphoglucomutase-2, malic enzyme-1, and superoxide dismutase-2, plus probable loci for major histocompatibility antigens near the q21-22 regions. An adenylate kinase and ABO blood group locus is tentatively assigned to chromosome 9, while genes for thymidine kinase and galactokinase are localized to the q21-22 band of chromosome 17. Linkage relationships of genes involved in the production of functionally related enzymes are also discussed. Multiple loci have been found for several enzymes catalyzing the same reaction, and genes determining certain mitochondrial enzymes are located on different chromosomes. Genes coding for lysosomal enzymes also appear to be scattered on different chromosomes throughout the human genom Linkage relationships between the human gene loci coding for certain functionally-related (sequential enzymes of the biochemical pathway of carbohydrate metabolism are illustrated, and show that close linkage is not necessary for coordinated functionin This is suggested as a universal phenomenon in the mammalian world. (72 references)

4225 REGULATION OF CELLULAR GROWTH. (Eng.) Pastan, I. (Natl. Cancer Inst., Bethesda, Md.). *Adv. Metab. Disord.* 8:7-16; 1975.

Current knowledge of the mechanisms regulating cellular growth is summarized. Current ideas of the mechanism of growth-promoting factors are largely generated from studies of insulin, most especially its effect on the metabolism of muscles, liver, and fat tissue. Prominent early actions of insulin are: increased transport processes, and decreased cyclic AMP (cAMP) levels. That cAMP regulates cell growth has been illustrated four ways: (1) agents raising cAMP levels slow cell growth, whereas (2) agents lowering cAMP levels promote growth, (3) cAMP levels vary directly with the doubling time of logarithmically growing cells, and (4) the highest cAMP levels are observed in density inhibited, nongrowing cells. Two stages of the cell cycle, at which cAMP acts to inhibit growth, are early G_1 and late G_2. Two types of response to insulin are observed: decreased adenylate cyclase activity, and increased cAMP phosphodiesterase activity. Likewise, two models of cAMP action suggested involve promotion of protein phosphorylation and induction of an allosteric change in a receptor protein. An effect of cyclic GMP on protein synthesis and poly(U)-dependent

henylalanine incorporation has also been noted. he metabolism of transformed cultured cells shows diminished requirement for exogenous growth factors, and resembles that of insulin- or serum-stimulated untransformed cells. In certain types f transformation, a change in a single membrane omponent regulating the interaction of growth actors with adenylate cyclase, cAMP phosphodiesterse, and specific transport proteins is suggested. 43 references)

226 EPITHELIAL CELLS: GROWTH IN CULTURE OF NORMAL AND NEOPLASTIC FORMS. (Eng.)
afferty, K. A., Jr. (Univ. Illinois at the Medical enter, Chicago, Ill.). *Adv. Cancer Res.* 21:249-73; 1975.

he division potential of different cell types *in ivo*, and factors possibly influencing the culturing f cells of different origins are discussed. Introictory remarks suggest a widespread (accidental) ontamination of common permanent human epithelial nes with HeLa cells, and imply a very infrequent pontaneous transformation of cultured human carnoma cells. A brief consideration of the nonithelial culture systems which experience routine itiation of cell strains notes the frequent sponneous degeneration of cultured fibroblasts and he search for species-related phenomena. The heory of cellular senescence, as observed for broblast cell lines, is also discussed. Obsertions of the relation of senescence and cell type te the unlimited *in vitro* division of some mouse ll cultures, the limited *in vitro* growth potenal of diploid fibroblasts from some organisms, d the euploidy revealed in several rat and rabbit parently permanent cell lines. Established dioid lines are also represented by lymphoid cells own in suspension culture; however, all human mphoblastoid lines thus far examined contain DNA the Epstein Barr virus and hence are probably oplastic. Examples of the development of normal ithelial cells in culture are also described. rmanent euploid epithelial cell lines are derived om teased *Rana sylvatica* tadpole fragments and tal lung tissue of the rat and ferret; however, ogressive heteroploidy is noted. Normal epielial cells in numerous short term culture are so reported, but indicate that deterioration of least some epithelial cells occurs. The paucity human carcinoma cells in culture is acknowledged. discussion of possible logarithmic (expanding) *vivo* epithelial cell populations considers facrs of clonal senescence and stem cell populations; near (renewing) cell populations are also condered. Investigations of the *in vivo* division tential of stratified squamous epithelia conder the factors of a quiescent subpopulation and external augmentation, while results of studies the intestinal epithelium suggest that the limits the division potential of fibroblasts may not ply in the case of all cell types. The relation tween karyology and growth potential is discussed, d suggests that neoplastic cells may be karyopically normal, sharply limited in division pontial, and normal in other key biological paraters. (85 references)

4227 GENOME COMPLEXITY AND *IN VIVO* TRANSCRIPTION IN HUMAN LEUKEMIC LEUKOCYTES. (Eng.)
Saunders, G. F. (M. D. Anderson Hospital and Tumor Inst., Houston, Tex. 77025); Chuang, C. R.; Sawada, H. *Acta Haematol. (Basel)* 54(4):227-233; 1975.

The composition of satellite DNAs and the transcriptional activity of the different kinetic classes of DNA are examined. At least eight well-defined satellites are isolated from the human genome. A tabulated summary of the physical properties of these human satellite DNAs, including buoyant densities in CsCl, chromosome location, and alkaline CsCl strand separation, is presented. In addition, studies reveal highly repetitive nonsatellite sequences arranged in blocks 1100 nucleotides long and interspersed with intermediate repetitive and nonrepetitive sequences greater than 2500 nucleotides long. Analyses of several classes of normal and leukemic human leukocytes find similar levels of unique DNA sequence transcription in the total cellular RNA; approximately 2.5-3.9% of the nonrepetitive sequences are thus represented. Assessment of repetitive sequence transcription *via in vitro* chromatin transcription and hybridization competition experiments with total cellular RNA shows chromatins from the most metabolically active cells are better templates. Hybridization of chromatin transcripts estimates 4.2-5.7% of the repetitive sequences are available for transcription. The results suggest greater differences among classes of human lymphocytes in the repetitive transcripts than in the nonrepetitive transcripts. It is further suggested that leukemia results from an impairment of the cell differentiation process, and that such impairment involves transcription of DNA sequences in malignant cells which are not transcribed in normally differentiated cells. (16 references)

4228 EXCISION REPAIR IN HUMAN CELLS. (Eng.)
Bootsma, D. (Dept. Cell Biology and Genetics, Erasmus Univ., Rotterdam, Netherlands); de Weerd-Kastelein, E. A. *Proc. Int. Cancer Congr. 11th.* Vol. 1 *(Cell Biology and Tumor Immunology).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 164-169.

General DNA repair mechanisms and specifically defective DNA repair in xeroderma pigmentosum (XP) are discussed; in addition, evidence suggesting a relationship between DNA repair and carcinogenesis is presented. Three cellular recovery systems are demonstrated in UV-exposed bacteria; photoreactivation, excision repair, and post-replication repair. Since "unscheduled DNA synthesis" (UDS) and "repair replication" have been demonstrated in human cells, it is assumed that an excision repair process also exists in human cells. The removal of UV-induced thymine dimers from the DNA of human cells has been demonstrated *via* chromatography, an immunological assay, and also through use of a dimer-specific endonuclease. The biological significance of such UDS and repair replication has been revealed through the discovery of their inhibition in XP. Following a discussion of the clinical characteristics of

XP, it is suggested that the phenotypic differences of the De Sanctis-Cacchione and the Hebra-Kaposi forms of the disease result from the variable expression of the same genetic defect. Exposure of XP cells to UV radiation results in low or negligible levels of UDS and repair replication, indicating a defect in the excision repair process; however, XP cells exposed to X-rays retain normal levels of UDS and repair replication. While it is thus inferred that the XP cells are defective in an early enzymatic step, several XP patients have not shown such a defect. Experimental evidence for genetic heterogeneity in patients is discussed. The combined data from biochemical analysis of XP cells and complementation results from cell fusion studies have indicated the involvement of at least five different genes. Such complementation groups are tabulated, and the involvement of a coordinated enzyme complex in the enzymatic repair mechanism is hypothesized. Such discoveries also suggest a causal relationship between defective DNA repair and carcinogenesis, and indicate that DNA repair processes may play a role in the cell transformation. (29 references)

4229 REGULATORS OF CELL DIVISION: ENDOGENOUS MITOTIC INHIBITORS OF MAMMALIAN CELLS. (Eng.) Lozzio, B. B. (Univ. Tennessee Memorial Res. Center and Hosp., Knoxville, Tenn.); Lozzio, C. B.; Bamberger, E. G.; Lair, S. V. *Int. Rev. Cytol.* 42: 1-45; 1975.

Antimitotic substances found in a variety of tissues and sera of humans and animals, and mitosis inhibitors produced by cultured cells are reviewed. The limitation of mitotic activity in high-density cultures cannot be explained solely on the basis of available nutrients. Specific and nonspecific inhibitors of cultured cell growth are reported. Crude extracts from murine embryo skin and placenta have retarded the growth of some carcinomas, spontaneous and transplanted tumors. Antimitotic substances were also found in extracts of human amniotic and chorionic membranes, and in molluscs and amphibian ovaries. Specific and nonspecific mitotic inhibitors partially purified from mammalian and amphibian kidneys have a lipoid composition, while the existence of a chalone is reported in amphibian kidneys. A variety of inhibitors have been isolated from liver tissue of various species; some fit the criteria for a liver chalone, while others are distinctly different in the biological properties. Such inhibitors have been intensively investigated for their effect on DNA, RNA, and protein synthesis. Some tissues of tumor-bearing animals and/or the tumor itself are found to contain mitotic inhibitors. Specific inhibitors of malignant cell multiplication extracted from tumors of rats, mice, and hamsters have included epidermal carcinoma, melanoma, lymphoma, and mylogenous leukemia. They are partially characterized as lipids, proteins, and polypeptides. Striated muscle extracts also contain components cytotoxic to malignant cells *in vitro* and *in vivo*. Tissue-specific epidermal chalones have been found to depress mitotic activity and DNA synthesis. Homologous antimitotic spleen factors are also reported and partially characterized. Growth regulatory factors have also been isolated from several other tissues. Sera from patients with neoplastic diseases and from women in the later stages of pregnancy strongly inhibit normal cell proliferation, whereas normal human sera have been found to be cytotoxic to atypical mammalian cells. A thermolabile, protein/lipoid component is the suspected cytotoxic agent. Thus mitotic inhibitors are variously identified as proteins, lipids, nucleic acid derivatives, and/or mucopolysaccharides. (250 references)

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4239 ONCOGENIC HERPES VIRUSES. (Eng.) Zur Hausen, H. (Inst. Clin. Virol. Univ. Erlangen-Nurnberg, Erlangen, West Germany). *Biochim. Biophys. Acta* 417(1):25-53; 1975. (232 references)

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4265 EPIDEMIOLOGY OF CANCER OF THE PROSTATE WITH SPECIAL EMPHASIS ON U.S.-JAPANESE COMPARISON (Jpn.) Maruchi, N. (Tokyo Univ. Sch. Medicine, Tokyo, Japan). *Gan No Rinsho* 21(3):137-147; 1975. (70 references)

4266 ENDOPLASMIC MEMBRANE AS A SOURCE AND A TARGET FOR CHEMICALLY REACTIVE METABOLIC INTERMEDIATES. (Eng.) Williams, D. J. (Dept. Biochemistry, Univ. Coll. London, Gower St., London WC1E 6BT, U. K.); Parry, G. *Biochem. Soc. Trans.* 3(1):69-72; 1975.

Reactive electrophilic intermediates generated *in vitro* by microsomal membrane preparations were examined for their effects on the membranes themselves. A good correlation between carcinogenicity and membrane degranulating activity of such intermediates was observed when membranes from livers of male Albino rats were incubated with fluorenylacetamide (20 μg/ml) in the presence of NADPH (1 mM) and/or Na_2SO_4 (1 mM). In contrast to the noncarcinogenic isomer (4-*N*-fluorenylacetamide) generated during incubation, the carcinogenic isomer (2-*N*-fluorenylacetamide) caused the removal of ribosomes from the membranes as shown by measurements of the RNA protein ratio after incubation. Membrane degranulation by 3,4-benzpyrene (10 μg/ml), monitored by following the unmasking of the thiol-disulfide-interchange enzyme, was dependent on added NADPH (1 mM) and was inhibited by CO and by 2-diethylaminoethyl-2,2-diphenyl valerate, supporting the view that microsomal hydroxylase is involved in the generation of species causing ribosome loss. 17-β-Estradiol (2 μg/ml) abolished the benzpyrene effect, while testosterone (2 μg/ml) afforded only partial protection. The effects of testosterone and 17-β-estradiol may be explained on the basis of an inhibition of benzpyrene metabolism. Since estradiol has been implicated in the activation of ribosome binding sites on the endoplasmic membranes of male rat liver, it is possible that such hormone-dependent ribosome-binding sites are attacked directly by chemically reactive metabolites generated locally in the membranes themselves.

4267 INVESTIGATION OF THE POSSIBLE INVOLVEMENT OF KETONIC DERIVATIVES OF POLYCYCLIC HYDROCARBONS IN HYDROCARBON CARCINOGENESIS. (Eng.) Dipple, A. (Chester Beatty Res. Inst., London, SW3 6JB England); Levy, L. S.; Iype, P. T. *Cancer Res.* 35(3):652-657; 1975.

The preparation, characterization, and biological activity of two isomeric K-region ketones derived from 7,12-dimethylbenz(*a*)anthracene (DMBA) are described. *Cis*-5,6-Dihydro-5,6-dihydroxy-7,12-dimethylbenz(*a*)anthracene was heated under reflux with glacial acetic acid and water. The orange precipitate formed on cooling was slurried with acetone, and the resultant pale yellow solid was dissolved in benzene and applied to a silica gel column. The isomeric ketones in fractions 8-14 were pooled, evaporated, and crystallized from benzene; the crystals were analyzed by mass spectrometry, UV absorption, and nuclear magnetic resonance; the isomer was identified as 5,6-dihydro-6-oxo-7,12-dimethylbenz(*a*)anthracene. Similarly, the isomer isolated from fractions 17-25 was identified as 5,6-dihydro-5-oxo-7,12-dimethylbenz(*a*)anthracene. These K-region ketones were applied to the shaved backs of male C57BL mice, injected sc into female CFLP mice, and incubated with hamster embryo cells *in vitro*. Chemical studies indicated that the primary products of the acid-catalyzed dehydration of *cis*-9,10-dihydro-9,10-dihydroxyphenanthrene, *cis*-4,5-dihydro-4,5-dihydroxybenzo(*a*)pyrene, and *cis*-5,6-dihydro-5,6-dihydroxy-7,12-dimethylbenz(*a*)anthracene were, in each case, the K-region phenols. The phenols of DMBA rearranged into the keto forms described above. The keto forms of the K-region phenols of DMBA were more stable than the enol forms. The K-region ketones of DMBA showed no carcinogenic activity *in vivo* and no transforming capacity *in vitro*. The data indicate that the K-region ketones of DMBA probably do not mediate the carcinogenic activity of DMBA.

4268 LOCALIZATION OF POLYCYCLIC HYDROCARBON CARCINOGENS IN THE LUNG FOLLOWING INTRATRACHEAL INSTILLATION IN GELATIN SOLUTION. (Eng.) Kennedy, A. R. (Harvard Sch. Public Health, Boston, Mass.); Little, J. B. *Cancer Res.* 35(6):1563-1567; 1975.

The deposition and localization of 1.6% benzo(*a*)-pyrene (BP) suspended in a 1.5% gelatin-0.9% NaCl solution was studied in male Syrian hamsters by UV fluorescence microscopy. The majority of BP particles were in the 0.5-1.0 μm size range. Changes in BP deposition were evaluated immediately after intratracheal administration of the BP suspension and at intervals of 1-2 hr, 24-48 hr, 5-7 days, and 2-4 wk to 3 mo. The BP particles were initially seen as intense white-yellow fluorescent particles distributed in the alveolar region as dispersed particles and occasional aggregates. At 1-2 hr, most particles were evenly distributed throughout the peripheral lung; some *in situ* metabolism of BP was suggested by the development in the peripheral lung of pale yellow fluorescent areas without distinct particles. Although large numbers of BP-filled macrophages were seen in the upper airways by 24 hr after instillation, little BP appeared to penetrate into the bronchial epithelium. After five days, few BP particles were left in the alveolar region; occasional clumps of particles were found in the peripheral lung macrophages and in the larger airways. Some of the pale yellow fluorescence that persisted in the peripheral lung appeared to be extracellular. After 2-4 wk, essentially no BP particles remained in the peripheral lung, macrophages, or larger airways. The pale yellow areas persisted in the peripheral lung, but their color was unstable on exposure to UV or tungsten light. These results differ from those previously obtained when BP was administered on small ferric oxide particles. Retention of BP was longer with the ferric oxide particles and the particles were deposited primarily on the epithelium of the larger airways. The BP-gelatin-0.9% NaCl solution technique appears to be a useful model for delivering the carcinogen dose to the alveolar region. As previously suggested by tumor induction experiments with 6.6-7.8% BP, this region is the major site of deposition and retention of the carcinogen.

4269 TEMPERATURE-SENSITIVE MUTANTS OF CHEMICALLY TRANSFORMED EPITHELIAL CELLS. (Eng.) Yamaguchi, N. (Columbia Univ. Coll. Physicians Surg., New York, N.Y.); Weinstein, I. B. *Proc. Natl. Acad. Sci. USA* 72(1):214-218; 1975.

The first isolation of temperature-sensitive (TS) mutants of epithelial cells transformed with chemical carcinogens was studied. The TS mutant, W-8, was obtained from K-16 normal epithelial rat liver cells exposed to 0.5 μg/ml *N*-acetoxy-2-acetylaminofluorene. When 10^5 or 10^6 W-8 cells were injected sc into newborn Sprague-Dawley rats, 1-2-cm locally invasive tumors composed of epitheloid cells appeared within 3-4 wk. The wild type W-8 clone was obtained by isolating a colony at 41 C in 1.2% methyl cellulose. Like the wild type W-8, the TS mutants readily grew in agar suspension at 36 C, but (in contrast to the wild type) they did not grow at 40 C. Detailed studies of one of the mutants (TS-223), which displayed the most extreme response to temperature, indicated that it also had reduced cloning efficiency at high temperature in monolayer culture and a lower saturation density. Scanning electron microscopy revealed that at 40 C, confluent cultures of TS 223 consisted of a monolayer of generally flat polygonal cells; at 36 C, the cultures contained many patches of piled-up cells that were spherical and had rougher surface membranes. All of these cellular changes were reversible with higher or lower temperatures. TS lesions appear to reside in a host cell gene that modulates expression of the transformed phenotype. When the 36 C and 40 C cultures were at their plateaus in saturation density, there was a very low level, of thymidine incorporation. A change to fresh medium at both 36 C and 40 C led to a burst of thymidine incorporation. While the TS mutants display minimal features of transformation complicating characterization, they may be useful in outlining minimal changes required for the expression of the transformed phenotype in epithelial cells.

4270 LACK OF INDUCTION OF DOMINANT LETHALS IN MICE BY ORALLY ADMINISTERED AF-2. (Eng.) Soares, E. R. (Natl. Inst. Environmental Health Science, Res. Triangle Park, N.C. 27709); Sheridan, W. *Mutat. Res.* 31(4):235-240; 1975.

Toxic and potential mutagenic effects of oral *trans*-2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2) were studied in C3H/HeJ, DBA/2J, and CBA/J mice. In the toxicity tests, AF-2, suspended in distilled water or 40% ethanol or dissolved in pure dimethylsulfoxide, was administered by gavage in doses of 200-900 mg/kg. There was no significant increase in deaths of AF-2-treated animals compared to controls unless mice were deprived of food and water for 24 hr prior to treatment. Starved mice died within 48 hr of receiving AF-2, and postmortem examination revealed a bright orange precipitate (probably AF-2) in the stomachs. In the dominant lethal tests, each of the total of 150 DBA/2J mice was treated, in groups of 30, with 300-450 mg/kg of AF-2 and paired with three C57BL/6J female mice for seven days. Pairing with other sets of three females was repeated for six consecutive weeks. Females were killed 17 days after initial contact with the male and examined for total number of implants and for postimplantation resorptions. In comparisons between control and treated groups, three variables were analyzed; (a) fertility (percentage of pregnant females), (b) number of implants per pregnant female, and (c) percentage of postimplantation deaths (based on resorptions per litter of each pregnant female). The results were analyzed by variance or nonparametric techniques. Only two comparisons proved significant: an increase in fertility in the group given 450 mg/kg AF-2 the first week, and a decrease in total implants in the 350 mg/kg group in the fourth week. AF-2 does not decrease male fertility or increase the rate of fetal death. AF-2 probably does not induce dominant lethals.

4271 QUANTITATIVE AUTORADIOGRAPHIC STUDIES ON THE COMPETITION OF DIETHYLNITROSAMINE (DENA) AND 9,10-DIMETHYL-1,2-BENZANTHRACENE (DMBA) IN THE LIVER CELL OF CBA-MICE. (Eng.) Amlacher, E. (Pathologisches Institut der Friedrich-Schiller-Universitat, 69 Jena, Ziegelmuhlenweg 1, East Germany); Danz, M. *Exp. Pathol. (Jena)* 10(5/6):338-347; 1975.

The competition of diethylnitrosamine and 9,10-dimethyl-1,2-benzanthracene, in CBA mice was studied by quantitative autoradiography. Animals received 0.012% diethylnitrosamine in drinking water; this dose was reduced by half 16 days prior to dimethylbenzanthracene injection, and was discontinued nine days before injection. Eighty-three days after the start of the experiment, the animals were injected ip with [^{3}H]-dimethylbenzanthracene. Control animals that received no diethylnitrosamine pretreatment were treated in the same way. Some of the pretreated and untreated controls were hepatectomized and injected ip with 30 μg [^{3}H]dimethylbenzanthracene 30 hr after two-thirds hepatectomy. Animals of all test groups were sacrificed eight hours after dimethylbenzanthracene injection. Histological liver sections from some of the animals that received diethylnitrosamine pretreatment and dimethylbenzanthracene injection were treated with perchloric acid to extract diethylnitrosamine/RNA. Paraffin sections of liver and ear skin were examined after fixation in Bouin's medium. The autoradiographs were exposed in the presence of $CaCl_2$, nine days for liver sections and 29 days for ear skin sections. During the precancerous phase in diethylnitrosamine-pretreated animals the rate of dimethylbenzanthracene incorporation into DNA/RNA and nuclear proteins was lower than the controls without diethylnitrosamine pretreatment. The rate of dimethylbenzanthracene incorporation into the cytoplasm was significantly enhanced in both pretreated and untreated hepatectomized animals; this may be related to the beginning of regeneration-enhanced RNA and protein synthesis. The ear skin did not show quantitatively demonstrable dimethylbenzanthracene incorporation, which may be explained by the lower rate of protein metabolism in the ear skin. It is concluded that changes in DNA/RNA following pretreatment with diethylnitrosamine occur at the same time as enzymatic changes, or may even precede them.

4272 HYPOTHETICAL DOSE--RESPONSE CURVES FOR CHRONIC EXPOSURES TO MUTAGENS OR CARCINOGENS SUBJECT TO SIMPLE ENZYMATIC DETOXIFICATION IN THE MAMMALIAN BODY. (Eng.) Bridges, B. A. (M.R.C. Cell Mutation Unit and Sch. Molecular Sciences, Univ. Sussex, Falmer, Brighton BN1 9QG, Great Britain); Stamper, J. G. *Mutat. Res.* 33(1):87-91; 1975.

A simple model is proposed for estimating the genetic risk associated with chronic exposure to mutagens or carcinogens subject to simple enzymatic detoxification in the mammalian body. Dose-response curves for chemical carcinogenesis and mutagenesis in the whole animal may be influenced by processes affecting the delivery of the applied dose to the target cell DNA or by processes affecting the response of the cell to the initial DNA damage. As an example of the former, one might assume a chronic exposure to a chemical mutagen whose reaction with DNA is first order with respect to the mutagen. This exposure would be assumed to result in an equilibrium situation and a simple enzymatic detoxification system (e.g., in the liver) which intervenes between the applied dose (e.g., the concentration in the blood coming from the gut) and the dose in the target organ (e.g., the gonad). Since the blood is a recirculating system, an equilibrium will be set up in which the concentration downstream of the detoxifying organ is always lower than the upstream concentration. As the upstream concentration decreases, the downstream concentration decreases to a greater extent, and, under certain circumstances as the applied dose is lowered, the delivered dose may become proportionately less than at high doses so that a new linear relation of lower slope is established. Such a biphasic curve is termed quasi-threshold to distinguish it from a true threshold. With such a model, the dose response for DNA damage at low doses is linear and may be extrapolated back until the biological effect merges with the "spontaneous" background; thus, there is a "no-effect" level of exposure. Where there is a single or predominant detoxification system, this model may be useful in estimating the genetic risk if the K_m and the effectiveness of the detoxifying organ can be measured experimentally.

4273 DNA REPAIR AS A POSSIBLE LINK BETWEEN CARCINOGENESIS AND MUTAGENESIS. (Eng.) Stich, H. F. (Cancer Res. Centre, Univ. British Columbia, Vancouver, Canada). *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, G. New York, American Elsevier, 1975, pp. 58-61.

Several studies of the direct relationship of DNA repair synthesis to the carcinogenic potential of chemicals are reviewed. The relationship has been applied to an *in vitro* screening procedure utilizing tissue cultures of mammalian fibroblasts. Among conditions which may alter the accuracy of the screen are: (1) the activating capacities of S-9 fractions from different tissues on precarcinogens (2) *in vitro vs in vivo* sensitivity of the target cells used in assay. The relevancy of the DNA repair test for carcinogenic potential is improved by applying multiple low doses of the carcinogens to the cell system. This approach more closely approximates the usual exposure in humans than the single large dose. It is suggested that several endpoints be used to determine carcinogenic potential of chemicals and/or viruses, i.e. DNA repair synthesis, chromosome aberration, incidence of neoplastic transformation. Based on tests with 80 chemicals, all carcinogens can be said to produce DNA lesions followed by a measurable level of DNA repair synthesis.

4274 ISOZYME PATTERN OF FRUCTOSE DIPHOSPHATE ALDOLASE DURING HEPATOCARCINOGENESIS INDUCED BY 2-ACETYLAMINOFLUORENE IN RAT LIVER. (Eng.) Silber, D. (Sch. Medicine, Pasteura 4, 50367 Wroclaw, Poland); Checinska, E.; Rabczynski, J.; Kochman, M. *Int. J. Cancer* 16(4):675-681; 1975.

Changes in the isoenzyme pattern of aldolase, during hepatocarcinogenesis induced by 2-acetylaminofluorene (AAF) in male Wistar rats, were studied. The rats were fed bread and, once/wk, carrots. In the group given 11.25 mg AAF/rat/day, the fructose-1,6-diphosphatase:fructose-1-phosphatase activity ratio increased from 1.47 after 4 mo, to 8.0 at 9.5 mo, compared to 1.2 for the control rats. After 9 mo of AAF administration, cholangioadenomas changing into malignant tumors were found. All of the A-B hybrid enzymes were demonstrated by electrophoresis at this time. These results support the hypothesis of dedifferentiation during neoplastic transformation.

4275 EVIDENCE FOR A SECOND ARYLHYDROXAMIC ACID ACYLTRANSFERASE SPECIES IN THE SMALL INTESTINE OF THE RAT. (Eng.) Olive, C. W. (Univ. Chicago Pritzker Sch. Medicine, Chicago, Ill. 60616); King, C. M. *Chem. Biol. Interact.* 11(6):599-604; 1975.

The possibility of existence of tissue-specific acyltransferase species was studied with antiserum to the enzyme. The small intestine of the Sprague-Dawley rat contains two species of arylhydroxamic acid acyltransferases. These enzymes were separated by gel filtration on Sephadex G-100. The smaller species had the mobility of rat liver acyltransferase and was precipitated with antiserum directed against the liver enzyme. The larger species was not precipitated with this antiserum and was not detected in the soluble fraction from liver. Both species showed greater activity with *N*-hydroxy-*N*-2-acetylaminofluorene than with *N*-hydroxy-*N*-4-acetylaminobiphenyl (*N*-hydroxy-AABP) as substrate. The smaller species showed more activity toward *N*-hydroxy-AABP than the larger species did.

4276 CONDITIONS MODIFYING DEVELOPMENT OF TUMORS IN MICE AT VARIOUS SITES BY BENZO(a)PYRENE. (Eng.) Vesselinovitch, S. D. (Franklin McLean Memorial Res. Inst., Univ. Chicago, Chicago, Ill. 60637); Kyriazis, A. P.; Mihailovich, N.; Rao, K. V. N. *Cancer Res.* 35(11/Part 1):2948-2953; 1975.

The modifying roles of age, sex, and strain of mice on the incidence, multiplicity, and spectrum of tumors induced by benzo(*a*)pyrene were investigated. The first-generation (F_1) hybrids of C57BL/6J x C3HeB/FeJ and C3HeB/FeJ x A/J mice of both sexes were given single ip injections (75 or 150 μg/g) of benzo(*a*)pyrene at 1, 15, or 42 days of age. Experimental animals were allowed to live their lifespans, while animals in control groups were killed at 52, 90, 142, or 170 wk of age. Animals treated with benzo(*a*)pyrene died, in general, by the 100th wk of age due to development of liver, lung, stomach, and lymphoreticular tumors. Few of the control animals died during that same observation period. The age of mice at the time of exposure to the carcinogen modified development of tumors at all the sites. The sex of animals influenced the development of liver and lymphoreticular tumors. The C3HeB/FeJ x A/J F_1 hybrids, developed lung tumors more readily than did the C57BL/6J x C3HeB/FeJ F_1 mice, which had significantly more liver tumors and neoplasms of the lymphoreticular system than the former strain. No strain difference was observed in regard to tumors at other sites. Higher doses of benzo(*a*)pyrene were more effective in inducing lung, liver, and stomach tumors. In addition, five cases of pancreatic ductal adenoma and adenocarcinoma were observed in carcinogen-treated mice. The data indicate that the preweaning animals are more sensitive to carcinogenic response than are the adults; the authors suggest that the relative cell immaturity, high rate of macromolecular synthesis, and a consequently high rate of cell replication, as well as low immunological competence, are probably causally related to the high susceptibility of these tissues to the inception of carcinogenesis.

4277 INHIBITION OF HEPATIC ARYL HYDROCARBON HYDROXYLASE BY 3-METHYLCHOLANTHRENE, 7,8-BENZOFLAVONE AND OTHER INDUCERS ADDED *IN VITRO*. (Eng.) Jellinck, P. H. (Dept. Biochemistry, Queen's Univ., Kingston, Ontario, Canada); Smith, G.; Newcombe, A.-M. *Chem. Biol. Interact.* 11(5):459-468; 1975.

The inhibition of aryl hydrocarbon hydroxylase by 3-methylcholanthrene, 7,8-benzoflavone, estrogens, and testosterone *in vitro* was investigated in liver microsomes from female Holtzman rats treated with 3-methylcholanthrene or 7,8-benzo-flavone (5 mg in 5 ml sesame oil, ip) 18 hr before sacrifice. A supernatant fraction of the liver (microsomes plus cytosol) was obtained at 8,000 x *g*. Microsomes from 50 mg liver were incubated with [12-^{14}C]-dimethylbenz(a)anthracene or [3,6-^{14}C]-benzopyrene (2 μg) and NADPH (0.3 mM) and one of the following: 3-methylcholanthrene and 7,8-benzoflavone at 2.5, 0.5, and 0.25 μg/ml; and estradiol-17β, diethylstilbestrol, and testosterone, at 2.5 μg/ml. Both 3-methylcholanthrene and 7,8-benzoflavone inhibited the metabolism of [12-^{14}C]-dimethylbenz(a)anthracene an [3,6-^{14}C]-benzopyrene by liver preparations from animals pretreated with the enzyme inducers but had little effect if the rats were untreated. With lower concentrations of tissue (5 mg) and [12-^{14}C]-dimethylbenz(a)anthracene (0.2 μg), as little as 0.025 μg/ml of 3-methylcholanthrene added *in vitro* to the liver fraction from 3-methylcholanthrene-treated rats produced a 35% decrease in the yield of water soluble metabolites. Estrogen or testosterone added to the incubation medium had no significant effect. A good correlation was observed between the ability of a compound to depress the formation of water-soluble metabolites and its *in vivo* aryl hydrocarbon hydroxylase inducing power. Strong inducers, such as 3-methylcholanthrene and benzopyrene gave values approaching that of preparations from untreated animals, whereas noninducers had virtually no effect in lowering the percentage of [12-^{14}C]-dimethylbenz(a)anthracene converted to water-soluble products. With [12-^{14}C]-dimethylbenz(a)anthracene as substrate, changes in metabolis were observed not only in the percentage converted to water-soluble products, but also in the nature o the ethyl acetate-soluble metabolites formed. It is suggested that 7,8-benzoflavone and those polycyclic hydrocarbons that are good inducers also have a hig affinity for the variant of cytochrome P-450 known as P-488; by combining with the cytochrome they compete with [12-^{14}C]-dimethylbenz(a)anthracene for th same site on the enzyme site resulting in a shift i the metabolism of dimethylbenz(a)anthracene toward that mediated by P-450.

4278 ARYL HYDROCARBON HYDROXYLASE INDUCTION IN MAMMALIAN LIVER-DERIVED CELL CULTURES. STIMULATION OF "CYTOCHROME $P_1$450-ASSOCIATED" ENZYME ACTIVITY BY MANY INDUCING COMPOUNDS. (Eng.) Owens, I. S. (Natl. Inst. Child Health Hum. Dev., Bethesda, Md.); Nebert, D. W. *Mol. Pharmacol.* 11(1):94-104; 1975.

Increases in aryl hydrocarbon (benzo[a]pyrene) hydroxylase activity were found in fetal rat liver primary cultures and in cell lines derived from rat Reuber Hepatoma H-35 or mouse Hepatoma BW 7756, after the cells were treated with any one of a lot number of hydrophobic compounds in the growth medium such as 3-methylcholanthrene, sodium phenobarbital, isoproterenol, α-naphthoflavone, β-naphthoflavone, 2,5-diphenyloxazole, 2-(4'-chlorophenyl)benzothiazole, 2-(4'-formylphenyl)benzothiazole, metyrapone, 1-(2-isopropylphenyl)imidazole, 2-diethylaminoethyl-2,2-diphenyl valerate HCL (SKF 525-A), piperonyl butoxide, diethylstilbestrol, sodium laurate, allylisopropylacetamine aniline, and aminopyrine. Generally, a dose slightly less than that which caused morphological changes indicative of cytotoxicity was the optimal inducing dose. The hydroxylase activity found in liver or hepatoma-derived cell cultures seemed to be more sensitive to inhibition in vitro by the α-naphthoflavone or 2,5-diphenyloxazole than by the metyrapone or SKF 525-A. It is also associated with a blue spectral shift in the Soret peak of

the reduced hemoprotein-CO complex. The phenobarbital-induced and basal hydroxylase activities in the liver of the intact adult animal are different from the PB-induced and basal enzyme activities in liver- or hepatoma-derived cell cultures; this indicated that cytochrome P_1450 was induced by some factor in the control medium or by phenobarbital in culture, whereas other P450 species predominated in the control or phenobarbital-treated adult intact animal. Therefore, for studies with liver- or hepatoma-derived cultures as experimental models for evaluating hepatotoxicity, drug metabolism, or chemical carcinogenesis by certain compounds known to be metabolized via the monoxygenase metabolic pathways, one must be cautious in the extrapolation of certain results found in cultured cells to the actual situation in the intact animal.

4279 SPECTRA OF PHENOLS OF BENZO(*a*)PYRENE IN FROZEN CRYSTALLINE SOLUTIONS AT 77 K AND THEIR USE FOR THE STUDY OF BENZO(*a*)PYRENE METABOLISM. (Rus.) Khesina, A. Ia. (no affiliation given); Khitrova, I. A.; Fedoseeva, G. E. *Zh. Prikl. Spektrosk.* 22(5):851-856; 1975.

Quasilinear fluroescence spectra of 3-OH-benzo*(a)*-pyrene (I) and 6-OH-benzo*(a)*pyrene (II) in frozen paraffin solutions were studied, and adapted to the study of benzo*(a)*pyrene (BP) metabolism in liver microsomal systems *in vitro*. Metabolism of I by rat microsomal polyvalent oxidases was demonstrated. Compound II was practically quantitatively metabolized in microsomal systems, i.e., it could not be regarded as the ultimate metabolite of BP. The rate of metabolism of BP into I by microsomal enzymes was not higher than 4%.

4280 USE OF SYNCHRONIZATION INDUCED BY CYCLOPHOSPHAMIDE IN A METHYLCHOLANTHRENE SARCOMA WITH CIRCADIAN PROLIFERATION TO RATIONAL SEQUENTIAL CHEMOTHERAPY. (Eng.) Focan, C. (Laboratoire d'Anatomie Pathologique, Universite de Liege, 1, rue des Bonnes Villes, B-4000 Liege, Belgium); Barbason, H.; Betz, E. H. *Biomedicine* 23(6):230-235; 1975.

The evolution of the mitotic activity in sarcoma T_{10} after the administration of a single dose of cyclophosphamide (CPA, 50 mg/kg, ip) and/or vinblastine (VBL, 2 mg/kg, ip) was studied in male C57BL mice grafted with T_{10} tumors. The drugs were administered at 8 am or 6 pm on the eighth day after tumor graftings. In one group, CPA was administered at 8 am on the eighth day after tumor grafting, and VLB was given at midnight on the ninth day. CPA alone had a significant antitumor effect, the morning injection being significantly more effective than the evening injection. VLB alone had no antineoplastic effect. When given at 8 am, CPA alone induced a prolonged inhibition of tumor mitoses that lasted for about 24 hr; mitoses then reappeared, with a peak observed at midnight on the ninth day, when the mitotic index was low in untreated tumors. After the tenth day, the normal circadian mitotic waves reappeared. When CPA and VLB were injected simultaneously, no significant antitumor effect was found. When a morning administration of CPA was followed by a midnight administration of VBL, a strong antitumoral effect was observed, the shrinkage of tumors being more marked after sequential CPA-VBL treatment than after CPA alone. However, the percentage of definite cures effected by CPA alone was not significantly increased by the sequential treatment. The results suggest that the relative synchrony normally induced in tumors by the circadian activity can be replaced by a much better synchrony, induced by an alkylating agent.

4281 INCREASED THYMIDINE UPTAKE BY METHYLCHOLANTHRENE-TREATED C3H/10T1/2 CELLS. (Eng.) Bairstow, F. (New York Univ. Medical Center, New York, N.Y. 10016); Heidelberger, C. *Int. J. Cancer* 16(3):370-375; 1975.

The uptake of ^{3}H-thymidine by postconfluent cultures of methylcholanthrene (MCA)-transformed C3H/10T1/2 mouse embryo cells was measured at time intervals up to 110 days following MCA treatment. MCA (1-15 μg/ml) was added to the cultures for 24 hr one day following seeding. In other experiments, ^{3}H-thymidine uptake was measured in mixtures of MCA-transformed and nontransformed 10T1/2 cells. In comparison with nontransformed cultures, the loss of tritium from the incubation medium was much greater with the MCA-transformed cells. The loss of tritium from the medium was well correlated with the uptake of ^{3}H-thymidine by the cells as determined by autoradiography. Tritium uptake was also considerably elevated above control (nontransformed) levels in admixtures containing 2% or 10% transformed cells; with more than 20% transformed cells in the mixture, there was no appreciable change in thymidine uptake. Measurements made at various intervals up to 110 days revealed that after 25 days the MCA-treated cultures incorporated significantly more thymidine than acetone-treated controls. The increased uptake corresponded with the appearance of Type III transformed foci in the MCA-treated cultures. The results suggest that thymidine uptake may eventually be used as an additional criterion of cell transformation.

4282 CHEMICAL CARCINOGENESIS IN DIFFUSION CHAMBERS. (Eng.) Parmiani, G. (Istituto Nazionale per lo Studio e la Cura dei Tumori, Via G. Venezian 1, Milan, Italy). *Proc. Int. Cancer Congr. 11th.* Vol. 2 *(Chemical and Viral Oncogenesis.* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 113-117.

Suitability of the diffusion chamber (DC) for the study of host-mediated chemical carcinogenesis and the immunogenicity of methylcholanthrene-induced tumors is investigated. Lung tissue of fetal mice was placed on the internal filters of the DCs, subsequently implanted ip in adult BALB/c mice. Five doses of urethane (1 mg/kg, ip) were administered to mice over a ten-day period. DCs were

transferred sc to immunodepressed (thymectomy plus 400 rads) BALB/c mice killed 8, 18, and 50 wk later In a similar experiment, fetal liver tissue from C3HF mice was placed in DCs, and a single dose of N-nitrosodimethylamine (4 μg/g, sc) was given to mice one week after ip implantation. DCs were transferred to immunodepressed C3HF mice which were killed at 8 and 16 wk. Histological examination of the lung and liver tissue in the DCs revealed no neoplastic transformation. Connective tissue predominated in most excised transplants. DCs were used to study the theory that the immunogenicity of tumors produced by carcinogenic transformed target cells depends on the stage of the cell cycle in which the target cell comes in contact with the chemical. BALB/c mice fibroblasts were placed on filters of DCs, then implanted ip in syngeneic mice. A filter with 30 μg 3-methylcholanthrene (MCA) was implanted (1) simultaneously and removed after one week (2) added to DCs after fourth week of implantation. At the end of fifth week, filters were transferred sc to BALB/c x C3HF mice. If MCA was in contact with fibroblasts during the first week of growth mice were more likely to develop sarcoma tumor nodules (16/62) than if the MCA was added at later stages (7/41). Early MCA contact resulted in 6/16 immunogenic tumors, whereas all tumors induced by fibroblasts subjected to late treatment with MCA were immunogenic, as tested by the growth excision method. The DC *in vitro-in vivo* technique can be used to study hydrocarbon carcinogenesis in immunologic experiments, but is not suitable for carcinogenic chemicals such as urethan or N-nitrosodimethylamine.

4283 INFLUENCE OF A CHRONIC ADMINISTRATION OF DIETHYLNITROSAMINE ON THE RELATION BETWEEN SPECIFIC TISSULAR AND DIVISION FUNCTIONS IN THE RAT LIVER. (Eng.) Van Cantfort, J. (Service de Chimie medicale, Universite de Liege, 151, Bd. de la Constitution, 4000 Liege, Belgium); Barbason, H. *Eur. J. Cancer* 11(8):531-536; 1975.

The relation between the division function and specific tissular function in the rat liver (which normally follow a circadian rhythm and are mutually exclusive, each predominating at a different point in the life cycle of the animal) was studied in diethylnitrosamine (DEN)-treated (10 mg/kg/day in the drinking water for 25 or 50 days) male Sprague-Dawley rats. At the end of DEN treatment, the animals were sacrificed, at 10 a.m. or 10 p.m., or were partially hepatectomized at 10 a.m. and then sacrificed 12-72 hr later. The mitotic index and the activities of cholesterol-7α-hydroxylase, benzopyrene-hydroxylase, and aminopyrine-*N*-demethylase were measured in the livers after sacrifice. In the DEN-treated animals, the mitotic index was 1% higher than in the normal controls, but no circadian rhythm of mitoses was detected. However, the circadian rhythm of cholesterol-7α-hydroxylase was either partially (25 days) or totally (55 days) abolished by the DEN treatment, the enzymatic activity reaching a steady state equilibrium intermediate between the highest and lowest values in the controls. After 55 days of drug treatment, the activity of aminopyrine-*N*-demethylase was decreased by about 50%, and that of benzopyrene-hydroxylase was almost completely inhibited. These changes were not reversed when drug treatment was discontinued ten days before sacrifice. After hepatectomy the mitotic index was increased, but the cholesterol-7α-hydroxylase activity was not inhibited. When partial hepatectomy was performed 25 days after DEN treatment, the first mitotic wave was reduced by 50%, and the mitoses evolved along the normal nycthermeral rhythm. When the operation was performed after 55 days, the number of mitoses stabilized at a level corresponding to 30% of the peak reached in the controls. The DEN-reduced activities of the drug-metabolizing enzymes were further reduced by partial hepatectomy. The results indicate that the antagonism between the division and specific tissular functions existing after hepatectomy and after DEN treatment alone, is completely deregulated when the surgery is performed in DEN-treated animals.

4284 FAILURE TO INDUCE TUMOURS IN GUINEA-PIGS AFTER CONCURRENT ADMINISTRATION OF NITRITE AND DIETHYLAMINE. (Eng.) Sen, N. P. (Health Protection Branch, Dept. Health and Welfare, Ottawa K1A OL2, Canada); Smith, D. C.; Moodie, C. A.; Grice, H. C. *Food Cosmet. Toxicol.* 13(4):423-425; 1975.

The effects of simultaneous administration of diethylamine hydrochloride (2 or 4 g/l) and sodium nitrite (0.4 or 0.8 g/l) in the drinking-water to male English short-hair guinea pigs was studied for a period of up to 30 mo. This treatment failed to induce any tumors in the experimental animals. However, 18 of 20 guinea-pigs given diethylnitrosamine (15 mg/l) in the drinking-water developed liver tumors within one year. None of the controls or animals receiving only the amine (4 g/l) or nitrite (0.8 g/l) developed liver tumors. The data suggest that the amount of *in vivo* synthesis of diethylnitrosamine from the ingested amine and nitrite occurring in the stomachs of the animals was insufficient to induce cancer in the animals within the experimental period. The strong basicity of diethylamine was probably responsible for the low *in vivo* yields of diethylnitrosamine.

4285 CHEMISTRY OF NITROSAMINES. II. SYNTHESIS OF α-FUNCTIONAL DIMETHYLNITROSAMINES. (Eng.) Wiessler, M. (Deutsches Krebsforschungszentrum, D-6900 Heidelberg, West Germany); *Tetrahedron Lett.* (30):2575-2578; 1975.

Synthesis of alpha-functional dimethylnitrosamines (chloromethyl-methyl-nitrosamine, dibenzylphosphate, nucleophilic substituents) is described. Dibenzylphosphate was converted to a dibenzylphosphoric acid methyl ester at room temperature in a few days. Attempts to synthesize toluene sulfonate resulted in the corresponding methyl ester. If the inter-

molecular transfer of the alkyl is possible in the presence of an adequate acceptor, this would indicate a correlation between the chemical reactivity of these esters and the biological effects of nitrosamines (alkylation of DNA).

4286 MUTAGENIC SELECTIVITY OF CARCINOGENIC NITROSO COMPOUNDS: II. *N.N*-DIMETHYLNITROSAMINE. (Eng.) Fahmy, O. G. (Royal Cancer Hosp., Fulham Road, London SW3 6JB Great Britain); Fahmy, M. J. *Chem. Biol. Interact.* 11(5):395-412; 1975.

The genetic properties of the hepatocarcinogen *N,N*-dimethylnitrosamine (DMN) were examined in *Drosophila* for the assessment of the role of dose, cellular metabolism and genic target in its mutagenicity. Genetic activity was assayed with respect to the induction of the nonspecific X-chromosome recessives (lethals and visibles) relative to the effects on specific genic sites, especially ribosomal DNA (rDNA), which yields *bobbed (bb)* mutations. Dose dependence followed a quadratic course for all mutational classes and germ cell types, which indicated that DMN induced at least some multiple-hit mutagenic events. The genetic activity of DMN was favored by cellular metabolism for all mutational classes, as was indicated by the progressive increase in mutation yield during spermatogenesis. The role of DNA methylation in the mutagenicity of DMN was deduced from quantitative assays of its genetic activity relative to the methylating nitrosamide *N*-methyl-*N*-nitrosourethane (MNUr) over the same dose range (1-10 m*M*) and on identical cell types and genic targets. In the metabolically inert cells (mature sperm), the two compounds were equally active with respect to the nonspecific effects (X-recessives), but MNUr was considerably more effective on rDNA (*bb*'s). Conversely, in the metabolically active cells (spermatocytes and spermatogonia), DMN exerted a much higher nonspecific mutagenicity than MNUr, but the two compounds were equally effective on rDNA. These results could not be entirely interpreted by the methylation hypothesis, and indicated that a DMN aldehydic metabolite, structurally analogous to MNUr, might be responsible for the induction of the rDNA mutations. The rDNA selectivity index of DMN was significantly lower than for MNUr, which paralleled their relative carcinogenic versatilities. However, DMN was comparatively more effective on the tRNA genes, a feature that might be associated with its oncogenic specificity.

4287 STUDIES ON LUNG TUMOURS: III. OXIDATIVE METABOLISM OF DIMETHYLNITROSAMINE BY RODENT AND HUMAN LUNG TISSUE. (Eng.) den Engelse, J. (Netherlands Cancer Inst., Amsterdam, The Netherlands); Gebbink, M.; Emmelot, P. *Chem. Biol. Interact.* 11(6):535-544; 1975.

The oxidative metabolism of dimethylnitrosamine (DMN) was studied in male mouse (C3Hf/A and GRS/A), Sprague-Dawley rat, and Syrian golden hamster respiratory tissues, as well as in primary lung neoplasia in humans. Prior to tissue removal, the animals were subjected for at least ten days to a light-dark regimen (start of 12-hr light period at 7 a.m.; tissues removed between 10:30 and 12:00 hr). [^{14}C]DMN was purified by Dowex-1-bisulfite column chromatography to remove a contaminant (probably [^{14}C]formaldehyde) interfering with the enzyme assay. Since formaldehyde and methyl carbonium ions (which yield methanol with water) are considered to be the primary products of DMN metabolism, tissue slices were assayed for the production of [^{14}C]CO_2 from ^{14}C-labeled methanol, formaldehyde, formate, and DMN. Oxidation of formate to CO_2 was very much rate-limiting, although the oxidation of formaldehyde to formate was not. This rate-limiting step was circumvented by introducing quantitative chemical oxidation of formate to CO_2 by mercury(II)chloride following the enzymic reaction. Since oxidation of methanol to CO_2 proved to be insignificant, production of CO_2 from DMN by lung enzymes and $HgCl_2$ may serve as a parameter for *N*-demethylating activity and the production of the suspected carcinogenically active methyl carbonium ions. The DMN-*N*-demethylating activities of lung tissue slices of the two mouse strains with widely different susceptibilities to formation of lung adenomas by DMN differed significantly, but the difference seemed too small to explain the divergence in tumorigenic response. The enzymatic activities decreased in hamster bronchus, hamster trachea, hamster lung, GRS/A mouse lung, C3HF/A mouse lung, human lung, and Sprague-Dawley rat lung, in that order. The reported resistance of the hamster respiratory system to tumor induction by DMN may therefore not be due to poor DMN-N-demethylating capacity.

4288 THE INACTIVATION OF BACTERIOPHAGE R17 BY ETHYLATING AGENTS: THE LETHAL LESIONS. (Eng.) Shooter, K. V. (Royal Cancer Hosp., London SW3 6JB Great Britain); Howse, R. *Chem. Biol. Interact.* 11(6):563-573; 1975.

The toxic action of ethyl methanesulphonate (EMS) and *N*-ethyl-*N*-nitrosourea (ENUA) on single-strand RNA was studied. Labeled ethylating agents [1-^{14}C]EMS (5.3 mCi/mM) and [^{3}H]ENUA (116 mCi/mM) were introduced into suspensions of bacteriophage R17 for periods of 16 and 2 hr, respectively. Unreacted reagents were separated from the bacteriophage on a Sephadex G-100 column. 3-Alkylcytosine, 7-alkylguanine, O^6-alkylguanine, 1-alkyladenine and 3-alkyladenine as well as various unidentified reactants were quantified as a fraction of the total bound radioactivity. At the mean LD for EMS, 8 M ethyl were bound per mole RNA, and for ENUA 3.5 M ethyl were bound. There was very little difference in the amount of alkylated products produced in experiments with methylating agents and EMS. However, ENUA was responsible for a greater production of 3-alkyladenine and unidentified reactants as well as a lowered production of 7-alkylguanine. Assuming that 7-alkylguanine is not a lethal lesion, the methylating

agents and EMS produce lethal lesions in the form of 3-alkylcytosine, O^6-alkylguanine, and chain breaks as a result of hydrolysis of ethyl phosphotriesters. These agents account for only .65 lethal lesions per molecule for ENUA. The possibility that 3-alkyladenine constitutes a lethal lesion for ENUA unlike the others is suggested.

4289 A MAMMALIAN SPOT TEST: INDUCTION OF GENETIC ALTERATIONS IN PIGMENT CELLS OF MOUSE EMBRYOS WITH X-RAYS AND CHEMICAL MUTAGENS. (Eng.) Fahrig, R. (Zentrallaboratorium fur Mutagenitatsprufung der Deutschen Forschungsgemeinschaft, D-7800 Freiburg Breisacherstr. 33, West Germany). *Mol. Gen. Genet.* 138(4):309-314; 1975.

The effects of X-irradation or of chemical mutagens on the expression of recessive color genes were studied. Embryos heterozygous for five recessive coat-color genes from the cross C 57 BL/6 J Han x T-stock were X-irradiated with 100 rads or treated *in utero* with 50 mg/kg methyl methanesulfonate (MMS) and ethyl methanesulfonate (EMS), respectively. Controls consisted of irradiated embryos of C 57 BL x C 57 BL matings homozygous wild-type for the genes under study, and nontreated offspring of both types of mating. The colors of the spots observed in the adult fur were either due to expression of the recessive coat genes or were white. Irradiated and mutagen-treated offspring of C 57 BL x T-stock matings had almost exclusively nonwhite spots, distributed randomly over the mouse surface. Irradiated offspring of C 57 BL x C 57 BL matings had only white spots which were always midventral. In nontreated offspring of both types of mating, no spot could be observed. After correcting for white midventral spots observed in the one type of control, the frequency of expression of one or the other of the recessive color genes was calculated to be about 11% for embryos irradiated with 100 rads at 11 days postconception, about 8% for embryos irradiated with 100 rads at 10 1/2 days postconception, about 1% for embryos irradiated with 100 rads at nine days postconception, about 7% for embryos treated with 50 mg MMS/kg at 10.5 days postconception, and about 8% for embryos treated with 50 mg EMS/kg at 10.5 days postconception. It is assumed that the white midventral spots are preferentially the result of pigment cell killing, while the nonwhite spots are preferentially the result of gene mutations or recombinational processes like mitotic crossing over and mitotic gene conversion. Of numerical and structural chromosome aberrations, only those come into question which are able to pass the filter of several mitoses. Therefore, the test system described is supposed to cover only heritable DNA-alterations, but the whole spectrum of them.

4290 HISTOLOGICAL CHANGES IN THE SUBMANDIBULAR GLANDS OF RATS AFTER INTRADUCTAL INJECTION OF CHEMICAL CARCINOGENS. (Eng.) Takeuchi, J. (Sch. Dent. Aichi-Gakuin Univ., Nagoya, Japan); Miura, K.; Katoh, Y.; Usizima, H. *Acta Pathol. Jpn.* 25(1):1-13; 1975.

Early histologic changes in the duct, acini, and interstitium of the salivary glands of male Donryu rats following injection of low doses of various carcinogens into the excretory canal of the submandibular gland are reported. The volumes injected were 0.02-0.03 ml. 20-Methylcholanthrene (5 mg/ml) induced squamous cell metaplasia and interstitial fibrosis initially, with a "benign lymphoepithelial lesion"-like pattern at three mo; dense hyalinization with a "mixed-tumor"-like pattern was observed at 4-5 months and epidermoid carcinoma and fibrosarcoma developed later. 9,10-Dimethylbenzanthracene (5 mg/ml) produced degenerative changes, squamous metaplasia, fibrosis, and inflammatory cell infiltration in the first two weeks followed by a high rate of carcinoma after 3-4 months of sarcoma after 7-8 months. 4-Nitr quinoline-N-oxide (5 or 10 mg/ml) resulted in dense hyalinization within 1-2 months and a high frequency of "mixed tumor"-like patterns. N-Nitroso-N-methyl urethane (10 mg/ml) and N-methyl-N-nitroso-N'-nitroguanidine (5 or 25 mg/ml) caused metaplastic changes, fibrosis, and lymphoid infiltration without neoplastic changes. Scarlet red (saturated solution in oliv oil) caused infiltration and aggregation of lymphoid cells with a "benign lymphoepithelial lesion"-like pattern but without neoplasm. The authors recommend the method of intraductal injection with various drugs as an adequate method to study the histologic changes by chemicals in the salivary glands of rats.

4291 STUDIES ON THE CYTOGENETIC ACTIVITY OF SOME COMMON FUNGICIDES IN HIGHER PLANTS. (Eng.) Zutshi, U. (Regional Res. Lab., Jammu 180001, India); Kaul, B. L. *Cytobios* 12(45):61-67; 1975.

The cytogenetic activities of 23 of the common brands of fungicide in use in India were studied using barley seeds (*Hordeum vulgare*) and secondary roots of *Vicia faba*. Sixteen of the fungicides tested (including copper fungicides, carbamates, inorganic and organic sulfur compounds, and mercurials) showed positive cytogenetic activity. In the barley, the most cytologically active compounds were Coppersan, Benlate, Lonocol, Dexon, Hexason, Cerasan, Karathane, and Morestan; these induced aberrations in 11.6-45% of the cells studied. The active ingredients in each of these fungicides are respectively: copper, butycarbamoyl-2-benzimidazole-carbamate; zinc ethyleneois thiocarbamate; *p*-dimethylamino benzene-diazosodium sulphonate; phenyl mercury chloride; ethyl mercury chloride; 2-1-methyl heptyl-4-6 dinitrophenyl crotonate; and 6-methyl-2-oxo-1,3-dithiole quinoxaline. Dexon, Copperson, and Karathane also induced high rates of seedling injury (50.74-53.23%), and Karathane reduced germination to 27.45% of control values. Most of the active fungicides induced more fragments than bridges, Karathane alone produced more bridges than fragments. The carbamates and mercurials produced abnormalities such as micronuclei, spindle distrubances, chromosome stickiness, and C-mitotic activities. Eight fungicides that showed significant radiomimetic activity in the barley seeds were further tested on the secondary roots of *Vicia faba*. All produced chromatid and isolocus breaks and chromatid exchanges, as well as aberrations such as fragments and gaps. It is concluded that Dexon, Benlate, Cerasan, Coppersan, Lonocol, Morestan, Hexason, and Karathane should be

assified as strong radiomimetic agents. They con-
itute important genetic and environmental hazards
en released into the ecosystem.

292 SOME OBSERVATIONS ON THE TOXICITY OF ADRIAMYCIN. (Eng.) Philips, F. S. Memorial Sloan-Kettering Cancer Center, 410 East 8th St., New York, N.Y. 10021); Gilladoga, A.; rquardt, H.; Sternberg, S. S.; Vidal, P. M. *Cancer Chemother. Rep. (Part 3)* 6(2):177-181; 1975.

e toxicity of the anti-tumor drug, adriamycin, was amined in rats and rabbits, and its tumorigenicity s studied in rats and in a cloned line of mouse broblasts. Female CD rats were given a single jection of adriamycin (5, 10, and 20 mg/kg). imals given 20 mg/kg died 4-9 days after injection; ose receiving 10 mg/kg died within less than 15 , after first suffering a steady weight loss. st rats receiving 5 mg/kg survived for at least e yr. Preterminal female rats, killed seven days ter receiving 20 mg/kg had severe lesions in the testine and hematopoietic organs, but no conspicu- s lesions occurred in the other thoracic and ab- minal viscera. Light microscopy showed no changes the kidneys of the rats at seven days after mg/kg. In the rats given a 5 mg/kg dose and lled 6-12 mo. later, glomerular damage was seen nsisting of focal thickening of the basement mem- ane and of the glomerular capsule. Groups of male bino rabbits received adriamycin as follows: 3 mg/ , 3 mg/kg one hour after an iv injection of digi- xin USP (30 μg/kg), 0.6 mg/kg/day for five succes- ve days, and 6 mg/kg, all at 4-wk intervals; and mg/kg at 3-wk intervals. Severe renal lesions re seen in almost all rabbits that received these ltiple doses. Of the 13 survivors in the first ree multiple-dose groups, 12 had chronic cardiac sions. Among the 14 survivors in the last two oups, 11 had such lesions. The pathologic effects re less advanced in the last two groups than in e first three. It is suggested that this was due the earlier time of killing in these two groups 3-18 wk and 7-15 wk respectively; first three oups killed after wk 28). If this assumption is rrect, it implies that the chronic lesion pro- esses steadily for long periods after cessation treatment with the drug. In tumorigenicity stud- s, female CD rats received one injection of either unorubicin (10 mg/kg or 5 mg/kg) or adriamycin mg/kg). The animals were killed when observable mors developed, when they appeared ill and were sing weight steadily, or at the end of one year. large number of benign mammary fibroadenomas and ssibly an increased incidence of mammary adeno- rcinomas were seen over control animals. Other lignant tumors in the treated animals included two classified subcutaneous tumors, one epidermoid rcinoma, and one liposarcoma in the daunorubicin oup, and one adrenal carcinoma in the adriamycin oup. Daunorubicin and adriamycin both transformed cloned line of mouse fibroblasts with a frequency uivalent to that of N-methyl-N-nitroso-N'-nitro- anidine.

93 EFFECT OF BCG ON DIMETHYLHYDRAZINE INDUCTION OF COLON TUMORS IN RATS. (Eng.) gers, A. E. (Mount Sinai Sch. Medicine, Class of 1978, New York, N.Y. 10029); Gildin, J. *J. Natl. Cancer Inst.* 55(2):385-391; 1975.

The effect of BCG injection into the colon wall (6.7 x 10^6 organisms) on the induction of colon tumors by 1,2-dimethylhydrazine dihydrochloride (DMH, 30 mg/kg intragastrically once weekly for five weeks) was examined in male Sprague-Dawley and Fischer Rats. Twenty-five rats received BCG alone; 21 were treated with BCG following the last dose of DMH; and five received BCG prior to DMH treatment. In 14 animals with DMH-induced colon tumors, BCG was injected directly into the tumors; in three rats with resected tumors, BCG was injected into the colon wall adjacent to the resection site. Animals treated with BCG alone developed a generalized infection that persisted for 21 wk. There was no mucosal ulceration or evidence of severe necrosis in either Sprague-Dawley or Fischer rats. Rats infected with BCG after DMH treatment developed colon tumors at the same rate and in the same incidence as in DMH-treated controls given Tween culture medium (7H9). However, 37% of the tumors in BCG-infected rats were mucinous adenocarcinomas, compared with 9% in rats given 7H9. Moreover, 47% of BCG-treated animals with colon tumors had metastases to the abdominal lymph nodes, the serosal surface of other gut segments, or (in one rat), the lung; metastases were rare in 7H9-treated rats. In many BCG-infected animals, primary or metastatic tumors were intimately associated with granulomas and acid-fast bacilli. The severity and persistence of BCG infection were enhanced in rats given DMH, compared with rats given BCG alone. Prior BCG infection had no effect on the induction of colon tumors by DMH, and no tumor metastasized. Only one of the five pretreated animals had evidence of infection when examined 45-59 wk after BCG injection. Direct injection of BCG into tumors had no effect on tumor size, although active infection and granuloma formation occurred; infection persisted in the adjacent colon and the abdominal lymph nodes. In animals subjected to tumor resection before intracolonic BCG injection, infection with BCG did not interfere with the healing of the colon or skin lesions.

4294 TUMOR INDUCTION STUDIES WITH *n*-BUTYL- AND *n*-PROPYLHYDRAZINE HYDROCHLORIDES IN SWISS MICE. (Eng.) Nagel, D. (Univ. Nebraska Medical Center, 42nd Street and Dewey Avenue, Omaha, Nebr. 68105); Shimizu, H.; Toth, B. *Eur. J. Cancer* 11(7):473-478; 1975.

Long-term studies on the tumor-inducing capabilities of *n*-butylhydrazine hydrochloride (BH) and *n*-propylhydrazine hydrochloride (PH) were undertaken. Solutions of 0.0125% BH and 0.025% PH were given separately and continuously in the drinking water of 6-wk-old, randomly-bred Swiss albino mice for the remainder of their lives. The lung tumor incidence was 53% in BH-treated and 49% in PH-treated animals, while the corresponding incidence in the untreated controls was 22%. Histopathological examinations of lung tumors revealed the characteristic appearance of adenomas and adenocarcinomas. The treatments had no apparent effect on the development of other types of neoplasms. The study demonstrates for the first time the tumorigenicity of

these chemicals. Because of widespread use of substituted hydrazines in the environment, their possible significance is discussed.

4295 *IN VIVO* CHROMOSOME-DAMAGING EFFECT OF CYCLOHEXYLAMINE IN THE CHINESE HAMSTER. (Eng.) van Went-de Vries, G. F. (Lab. Pharmacology and Toxicology, Natl. Inst. Public Health, P. O. Box 1, Bilthoven, The Netherlands); Freudenthal, J.; Hogendoorn, A. M.; Kragten, M. C. T.; Gramberg, L. G. *Food Cosmet. Toxicol.* 13(4):415-418; 1975.

The chromosome-breaking activity of cyclohexylamine (CHA) was tested by oral administration of the chemical in 20 Chinese hamsters. The hamsters were treated po with CHA of high purity given in three daily doses of 200 mg/kg/day. The purity of the CHA was checked by mass spectrometry and in view of the instability of this compound, it was found advisable to handle it at a low pH (2.2-2.4) and in a nitrogen atmosphere. Chromosome analysis was carried out on phytohemagglutinin-stimulated lymphocytes of the peripheral blood before and after the administration. A significant increase ($P < 0.0005$) in the number of structural aberrations of the chromosomes was found after the treatment. A ring chromosome, several exchange figures and numerous fragments and breaks were registered. Because the lymphocyte cultures necessitate removal of a large volume of blood from the hamsters, the influence of hematopoiesis on the number of chromosome aberrations is questioned.

4296 PATHOLOGIC ANALYSIS OF CHEMICAL NEPHRITIS IN RATS INDUCED BY *N*-(3,5-DICHLOROPHENYL)SUCCINIMIDE. (Eng.) Sugihara, S. (Nagoya City Univ. Medical Sch., Mizuho-ku, Nagoya 467, Japan); Shinohara, Y.; Miyata, Y.; Inoue, K.; Ito*, N. *Lab. Invest.* 33(3):219-230; 1975.

The effects of N-(3,5-dichlorophenyl)succinimide (NDPS) administration to 78 male Wistar rats were studied by blood chemical, histopathologic, histochemical, and ultrastructural examinations. NDPS was given to 72 rats in drinking water for 4, 8, 12, 16, 20, and 24 wk; the remaining rats served as untreated controls. Administration of 5,000 ppm NDPS induced severe damage of the kidneys, but did not affect other organs. Administration of 2,500 ppm NDPS had little effect, even on the kidneys. Chemical analysis of the blood showed that the urea nitrogen level increased with the increase in the period of NDPS administration. Histopathologic examination showed intensive cell infiltration, mainly of lymphocytes, into the renal interstitium after NDPS administration for only four weeks. After NDPS administration for 12 wk or more, typical interstitial nephritis was observed. Histochemical analysis showed that after only one week various enzymatic activities in the proximal convoluted tubules were markedly decreased whereas their activities in the distal convoluted tubules were relatively well preserved for at least four weeks. These results indicate that NDPS predominantly attacked the proximal convoluted tubules. After four weeks, the most prominent ultrastructural changes were seen in the proximal convoluted tubules where the epithelial cells lost their polarity and had a very abnormal arrangement. These cells showed well developed, edematous microvilli, poorly developed basal infoldings, swollen mitochondria of various sizes, aggregated β-type glycogen granules, and debris of RBC. Development of the endoplasmic sizes, aggregated β-type glycogen granules, and debris of RBC. Development of the endoplasmic reticulum, Golgi complex, ribosomes, and lysosomes was poor in the cytoplasm. These investigations indicate that NDPS affects the function of the proximal convoluted tubules. NDPS is a selective nephrotoxic substance. That is, it initially damage the proximal convoluted tubules, and subsequently causes interstitial nephritis. It is suggested that nephritis induced by NDPS is useful as a model of interstitial nephritis in man.

4297 URINARY METABOLITES OF 2,5,2',5'-TETRACHLOROBIPHENYL IN THE NONHUMAN PRIMATE. (Eng.) Hsu, I. C. (Univ. Wisconsin Medical Sch., Madison, Wis. 53706); Van Miller, J. P.; Seymour, J. L.; Allen, J. R. *Proc. Soc. Exp. Biol. Med.* 150(1):185-188; 1975.

Four metabolites of 2,5,2',5'-tetrachlorobiphenyl (TCB) were isolated from the urine of infant nonhuman primates. [^{3}H]TCB (6.1 μCi/mg) was injected by gastric intubation into four male infant rhesus monkeys. After 72 hr the monkeys were sacrificed, and urine was collected and analyzed by thin layer chromatography, gas liquid chromatography, and mass spectrometry. TCB, monohydroxy-TCB (I), dihydroxy-TCB (II), hydroxy-3,4-dihydro-3,4,-dihydroxy-TCB (III), and *trans*-3,4,-dihydro-3,4,-dihydroxy-TCB (IV) were all identified in the urine. Of the above metabolites, only I and IV have been identified in lower animals. None of the above has been isolated in primates to this time. Production of the metabolites, particularly III and IV, strongly suggests that the metabolic mechanism works through arene oxide intermediates, which are known mutagens.

4298 THE EFFECTS OF THE CONTINUOUS ADMINISTRATION OF *N,N*-DIMETHYL-4-PHENYLAZOANILINE (DAB) ON THE ACTIVITIES AND THE INDUCIBILITIES OF SOME DRUG-METABOLIZING ENZYMES IN RAT LIVER. (Eng.) Autrup, H. (Univ. Nairobi, Medical Sch., P.O. Box 30588, Nairobi, Kenya); Thurlow, B. J.; Warwick, G. P. *Chem. Biol. Interact.* 11(5):313-328; 1975.

The effect of feeding male Porton Wistar rats a 10% protein diet containing 0.06% *N,N*-dimethyl-4-phenylazoaniline (DAB) for 29 wk on the activity of DAB-azoreductase, nitroreductase (*p*-nitrobenzoic acid), *N*-oxidase (*N,N*-dimethylaniline), *N*-demethylase (DAB), cytochrome P-450, NADPH-cytochrome *c* reductase, β-glucuronidase and arylsulphatase A was studied. Rapid decreases occurred in the activities of the first six enzymes, reaching minimal values at between 4 and 8 wk. Activities then increased in all cases to control or nearly control levels. This rate of increase was least for cytochrome P-450. At four weeks, azoreductase activity with the chemotherapeutic agent CB10-252(I) as substrate was significantly higher

than in control rats. Early increases occurred in the activities of β-glucuronidase and arylsulphatase A and the activity of the latter never dropped below the control level. The effect of phenobarbital (100 mg/kg) pretreatment on the DAB-fed rats was studied at four-week intervals. The activities of DAB-azoreductase and of nitroreductase increased throughout the whole period, while the activities of the lysosomal enzymes were decreased. After feeding DAB for four weeks, the effect of ip injections of phenobarbital (100 mg/kg) and 3-methylcholanthrene (40 mg/kg) on the activities of DAB-azoreductase, CB10-252-azoreductase and components of the azoreductases (cytochrome P-450, NADPH-cytochrome *c* reductase, the CO-sensitive pathway, and the NADH-dependent pathway) were studied. The activity of CB10-252-azoreductase was not induced by phenobarbital or 3-methyl-cholanthrene, and CO did not inhibit its reduction. Its reduction depended only slightly on NADH. CO caused a greater relative decrease in the activity of DAB-azoreductase in dye-fed animals and also in animals following PB and MC pretreatment, implying a greater role of cytochrome P-450 in dye-fed animals.

4299 MELOCHINONE, A NOVEL QUINOLINONE FROM *MELOCHIA TOMENTOSA* L. (Eng.) Kapadia, G. J. (Coll. Pharmacy and Pharmacal Sciences, Howard Univ., Washington, D.C. 20059); Paul, B. D.; Silverton, J. V.; Fales, H. M.; Sokoloski, E. A. *J. Am. Chem. Soc.* 97(23):6814-6819; 1975.

Melochinone ($C_{22}H_{21}NO_2$) was obtained by chromatography on silicic acid from a benzene extract of the root constituents of the tumorigenic plant *Melochia tomentosa*. The melochinone was studied by elemental analysis, mass spectrometry, chemical ionization with isobutane, UV spectrometry, and nuclear magnetic resonance (NMR), and X-ray crystallography. Its melting point was 316-318 C, and it was found to be a neutral compound which was insoluble in aqueous acid and alkali and inert to the action of boiling 10% alcoholic hydrochloric acid and 5% boiling alcoholic potassium hydroxide. It was recovered unchanged from lithium aluminum hydride in tetrahydrofuran and could not be dehydrogenated with Pd on charcoal at 350 C. The UV spectrum suggested an extended aromatic system; the NMR spectrum suggested an allylic methylene-methine configuration and the presence of an $X-CH_2CH_2CH_2CH=C<$ fragment, an olefinic C methyl group, a methoxyl group, and a phenyl group. X-ray crystallography using direct methods gave the structure 2-methoxy-6-methyl-7-phenyl-9,10,11-trihydro(4*H*)cyclohepta-[*f*]quinolinone.

4300 CAFFEINE INHIBITS CELL TRANSFORMATION BY 4-NITROQUINOLINE-1-OXIDE. (Eng.) Kakunaga, T. (Natl. Cancer Inst., Bethesda, Md. 20014). *Nature* 258(5532):248-250; 1975.

The effect of caffeine on the transformation frequency of A31-714 mouse cells, a subclone isolated from BALB/3T3-A31 clone, treated with 4-nitroquinoline-1-oxide was investigated. Actively growing cells were treated with 4-nitroquinoline-1-oxide (0.1 μg/ml) for 30 min in suspension, washed, and plated at an inoculum such that 1 x 10^4 cells/5-cm dish survived for the transformation assay and 30-100 cells/dish survived for the assay of plating efficiency. Caffeine was present in the culture medium for the first 48 hr after plating. The medium was then replaced with fresh, caffeine-free medium, and was changed twice a week. Dishes were fixed with methanol and stained with Giemsa either 10 or 30 days after plating and scored for plating efficiency and transformation frequency, respectively. In the first 48 hr after treatment, caffeine reduced the survival of treated cells but not that of untreated cells. Transformation frequency per surviving cell was also reduced by caffeine. Both survival and transformation frequency of treated cells were inversely proportional to the concentration of caffeine. The inhibitory effect of caffeine on transformation frequency was also dependent on the concentration of 4-nitroquinoline-1-oxide. The exposure of cells to caffeine either before or 48 hr after treatment with 4-nitroquinoline-1-oxide had no marked effect on survival or on transformation frequency. It is suggested that the reduction of survival and transformation frequency caused by caffeine in 4-nitroquinoline-1-oxide-treated A31-714 cells is related to the observation that caffeine inhibits postreplication repair in mouse cells. The results support the somatic mutation theory of cell transformation.

4301 PANCREATIC ISLET-CELL AND OTHER TUMORS IN RATS GIVEN HELIOTRINE, A MONOESTER PYRROLIZIDINE ALKALOID, AND NICOTINAMIDE. (Eng.) Schoental, R. (Royal Veterinary Coll., Royal Coll. St., London NW1 England); *Cancer Res.* 35(8):2020-2024; 1975.

The long term effects of the monoester pyrrolizidine alkaloid, heliotrine were studied in 34 weanling Porton-Wistar rats pretreated with nicotinamide. Three of six male rats, surviving 22-27.5 mo after one or two intragastric doses of heliotrine (230 mg/kg body wt), and nicotinamide (350 mg/kg body wt, developed pancreatic islet-cell tumors, accompanied in one of the rats by transitory cell papillomas of the urinary bladder and interstitial testicular tumors and in another by a hepatoma. The lesions in the livers showed progression from megalocytosis, to microscopic hepatocellular hyperplasia, to increasingly larger nodules and hepatoma. One rat, given heliotrine but no nicotinamide, also developed adenoma of the pancreatic islet cells. Heliotrine, in which the crucial double bond in the pyrrolizidine moiety is sterically hindered, appears to be less readily sequestered by the liver and also to affect other organs. Alkylation of nicotinamide at the N-1 position prevents its being reused for coenzyme biosynthesis. Hence, pretreatment of rats with large doses of nicotinamide prevents the depletion of nicotinamide adenine dinucleotide coenzymes and liver necrosis in rats given heliotrine (230 mg/kg).

4302 DEHYDRORETRONECINE-INDUCED RHABDOMYOSARCOMAS IN RATS. (Eng.) Allen, J. R. (Univ. Wisconsin Medical Sch., Madison, Wis. 53706); Hsu, I. C.; Carstens, L. A. *Cancer Res.* 35(4):997-1002; 1975.

Two groups of 75 male Sprague-Dawley rats were given sc injections of either monocrotaline (5 mg/kg) or its major detectable metabolite, dehydroretronecine (20 and 10 mg/kg), biweekly for one yr. Tissues obtained from partial hepatectomies performed at four mo on a portion of these animals showed that both compounds caused a decided inhibition of mitotic division in regnerating liver. Rhabdomyosarcomas developed at the site of dehydroretronecine injection in 51.6% of the rats and in 3.3% of the monocrotaline-treated rats. Metastatic lesions were recorded in 8.3% of these animals. In addition, 10% of the monocrotaline-treated rats developed other tumors that included myelogenous leukemias, hepatocellular carcinomas, and pulmonary adenomas. These data indicate that either monocrotaline or its metabolite dehydroretronecine are capable of causing neoplastic transformation in the tissues of experimental animals.

4303 BIOCHEMICAL CHANGES IN GR MOUSE MAMMARY TISSUE DURING HORMONAL TUMOR INDUCTION. (Eng.) Daehnfeldt, J. L. (Fibiger Laboratory, Ndr. Frihavnsgade 70, 2100 Kobenhavn, Denmark); Schulein, M.; Briand, P. *Eur. J. Cancer* 11(7):509-515; 1975.

Changes in glucose-6-phosphate dehydrogenase (G-6-PDH) and lactose synthetase (LS) activity, and in hormone receptor capacity, occurring during hormonal induction of GR mouse mammary tumors were studied; these parameters were compared in tumorous and nontumorous tissue from the same animals. Treatment of spayed 10-12 wk-old virgin GR mice with estrone (0.5 μg/ml in drinking water) and progesterone (5-10 mg sc pellets weekly) led to mammary tumor development after about 12 wk. Pronounced tissue changes, however, were observed during the first three weeks after the start of hormonal treatment. The total weight of the glands more than doubled during this period, while the protein/DNA ratio decreased. G-6-PDH activity rose by 25% during the first two weeks of hormonal treatment calculated on a protein basis, but fell again to the initial value during the remainder of the induction period. LS A-protein activity and B-protein content rose to a steadily high level after two weeks of treatment. The non-blocked cytoplasmic estradiol binding capacity decreased after hormonal treatment of spayed virgins. In the induced tumors, the RNA/DNA ratio was unchanged, and the protein/DNA ratio decreased by 25% compared to nontumorous mammary tissue from the same mice. The activity of G-6-PDH increased by 50% as calculated on a protein basis. The increased LS A-protein activity remained unchanged, while LS B-protein disappeared. There was ten times as much non-blocked cytoplasmic estradiol receptor protein as in the nontumorous tissue from the same animals. These experiments show that high estradiol receptor content and undetectable levels of LS B-protein are characteristic changes in the horomone-induced GR mouse mammary tumors.

4304 COVALENT BINDING OF *TRANS*-STILBENE TO RAT LIVER MICROSOMES. (Eng.) Docks, E. L. (U.S. Borax Res., Anaheim, Calif.); Krishna, G. *Biochem. Pharmacol.* 24(21):1965-1969; 1975.

Trans-stilbene, a weak synthetic estrogen previously shown to be hydroxylated in several animal species, was investigated to determine if it covalently binds to tissue macromolecules. Liver damage was also evaluated histopathologically. Studies *in vitro* showed that ^{14}C-*trans*-stilbene (0.1 M) became covalently bound to Sprague-Dawley rat liver microsomes and that the covalent binding was linear for at least 20 min. The rate of covalent binding of *trans*-stilbene was not altered by pretreating rats with phenobarbital (80 mg/kg, ip) but was markedly increased by pretreatment with 3-methylcholanthrene (20 mg/kg, ip). Oxygen and NADPH were necessary for binding. Carbon monoxide inhibited covalent binding to microsomes from nonpretreated rats by 95%, with microsomes from phenobarbital- and 3-methylcholanthrene-pretreated rats, the inhibition was 60% and 27%, respectively. After *in vivo* administration of ^{14}C-*trans*-stilbene (400 mg/kg, ip), the estrogen was covalently bound to liver, fat, kidney, plasma, lung and heart of untreated or phenobarbital- or 3-methylcholanthrene-pretreated animals. The liver contained the greatest amount of covalently bound material, and the heart contained the least. 3-Methylcholanthrene pretreatment increased the covalent binding of *trans*-stilbene, especially to liver and plasma. *Trans*-stilbene administered at doses of 100-800 mg/kg did not cause any liver or kidney histopathological abnormalities. Administration of phenobarbital or 3-methylcholanthrene before *trans*-stilbene injection (200 mg) also did not result in any abnormalities in liver or kidney tissues. Glutathione did not seem to act as a protective substance because after the complete removal of this substance by diethyl maleate *trans*-stilbene did not damage kidney or liver tissues. Although *trans*-silbene binds covalently to tissue macromolecules, this binding apparently does not lead to hepatotoxicity.

4305 THE SIGNIFICANCE OF ADENOSIS AND CLEAR-CELL ADENOCARCINOMA OF THE GENITAL TRACT IN YOUNG FEMALES. (Eng.) Herbst, A. L. (Adenocarcinoma Registry, Warren 275, 275 Charles St., Boston, Mass. 02114); Scully, R. E.; Robboy, S. J. *J. Reprod. Med.* 15(1):5-11; 1975.

An up-dated analysis of 170 cases of clear-cell adenocarcinomas of the genital tract occurring in females born after 1940 is presented. Histories of pre-natal medication of their mothers reveal dosage with non-steroidal synthetic estrogen, diethylstilbestrol (DES), in 95 cases and non-specified treatment for bleeding or miscarriage in 19 cases. Amount or duration of dosage does not appear significant in development of the adenocarcinomas. Complete maternal records note treatment was always initiated prior to 18th wk of pregnancy, indicating the importance of timing of treatment. Age of carcinoma cases at time of diagnosis ranged from seven to 27 yr. Asymtomatic cases had small tumors and no recurrences in contrast to those with presenting symptoms of bleeding or discharge. Radiation and surgery have been employed in therapy, but even in a four-year period of study, 24 cases have died and 13 have had recurrences. A few partial remissions but no regressions have occurred as a result of the use of chemo-

therapeutic agents such as 5-fluorouracil or the vinca alkaloids. Screening examinations of females exposed to DES are recommended at the time of menarche or by the age of 14 and should include inspection and palpation of the vagina and cervix and iodine staining. Use of the colposcope may be valuable but is not crucial. Biopsy-proven adenosis has been found in one-third or more screened asymptomatic DES-exposed females. Reports of higher incidence may be attributed to differing interpretations of the boundary between the vagina and cervix. In many DES-exposed girls, the boundary is indistinct due to congenital deformities of the upper vagina and cervix. Excision of all areas of vaginal adenosis in DES-exposed females is not recommended, however continuous follow-up appears desirable.

4306 MORPHOLOGICAL ALTERATIONS OF THE CERVICAL MUCOSA AND OF THE SQUAMOUS EPITHELIUM OF THE PORTIO IN WOMEN WHO USE OVULATION INHIBITORS AND IN THOSE WHO USE NONE. (Ger.) Herting, W. (Rheinischen Landesfrauenklinik, 56 Wuppertal 1, Vogelsangstrasse 106, West Germany); Schnell, J. D. *Fortschr. Med.* 93(4):176-178; 1975.

Morphological changes of the cervical mucosa and of the squamous epithelium were studied in 262 patients with precancerous lesions of these organs to establish the influence of hormonal ovulation inhibitors on the changes and on age at manifestation. Dysplasia was diagnosed in 31 patients, carcinoma *in situ* in 98 patients, microcarcinoma in 8 patients, and carcinoma in 125 patients. After elimination of patients aged over 45 yr, most of whom are unlikely to use ovulation inhibitors due to advanced age, there was no significant difference in the age of manifestation of the lesions between patients who had been using ovulation inhibitors and those who had not. Comparative histomorphological investigations on 40 patients who had been using ovulation inhibitors for at least one year and in 40 patients who had not used such preparations revealed that precancerosis, basal hyperactivity, a tendency toward keratinization of the squamous epithelium, as well as hyperplasia of reserve cells, distinct proliferation of cervical glands, and intense mucus formation in the cervical mucosa were more frequent and pronounced in patients who had been using ovulation inhibitors than in those who had not.

4307 NODULAR TRANSFORMATION (NT) OF THE LIVER AND INTRAHEPATIC HEMORRHAGE IN WOMEN ON ORAL CONTRACEPTIVES [abstract]. (Eng.) Stauffer, J. Q. (Upstate Medical Center, Syracuse, N.Y.); Lapinski, M. W.; Honold, D. J.; Myers, J. K. *Gastroenterology* 68(4):991; 1975.

Three cases of young women on birth control pills (BCP) developing solitary hepatic nodules are reported. A 25-yr-old woman had been on a variety of BCP for seven years; the patient noted a large mass in her lower abdomen. A large pedunculated tumor extending from the surface of the left lobe of the liver was found and resected. The tumor was encapsulated and there was marked increase in vascularity. A 29-yr-old woman who had been taking BCP for six years, noted a mobile, nontender mass in her abdomen. At exploration, a large tumor mass was found in the left lobe of the liver and a partial left hepatectomy was performed. Microscopically, the hepatocytes were well differentiated and no increase in bile ducts or blood vessels was noted. A 29-yr-old woman who had been on BCP for six years presented with sudden onset of right upper quadrant pain, fever and precipitous anemia. A large hematoma was found in the right lobe of the liver. This syndrome must be considered in young women on BCP who present with abdominal pain as this may represent massive intrahepatic or intraperitoneal hemorrhage. Diagnosis is established by palpation of a mass, an abnormal liver scan, angiography or peritoneoscopy. Large tumors must be resected and continued use of BCP is contraindicated.

4308 LIVER TUMORS IN WOMEN ON CONTRACEPTIVE STEROIDS. (Eng.) Christopherson, W. M. (Health Sciences Center, Louisville, Ky. 40201); Mays, E. T.; Barrows, G. H. *Obstet. Gynecol.* 46(2): 221-223; 1975.

Of 13 cases of liver tumors in young women who had taken oral contraceptives for 1-8 yr, eight were focal nodular hyperplasia. One of the patients died of hemorrhage from a ruptured benign hepatoma during pregnancy. One case was a liver cell carcinoma which also bled. Physicians involved in the care of persons taking oral contraceptives should be aware of this possible complication, which usually presents with evidence of acute abdomen.

4309 SPUTUM CYTOLOGY AMONG FREQUENT USERS OF PRESSURIZED SPRAY CANS. (Eng.) Good, W. O. (Montrose Mem. Hosp., Colo.): Ellison, C.; Archer, V. E. *Cancer Res.* 35(2):316-321; 1975.

Sputum cultures were taken among frequent users of aerosol spray cans and among other persons to determine if aerosol preparations alter the flora of the bronchial tree or contain carcinogenic agents. Sputum samples were taken from 50 white adult patients, "frequent users", from 200 white adult patients in the same geographical area, and from 50 white nonpatients from another geographical area. An attempt was made to match each of the individuals in the "frequent users" group with a similar person from the other two groups on the basis of age, sex and cigarette-smoking habits. All three groups of samples were collected in 50% ethanol solution containing 2% polyethylene glycol 1540, sent to the same cytology laboratory, and treated identically. Each sputum sample was classified on the basis of the most atypical cell seen. Atypical metaplastic changes in exfoliated cells were compared between the groups. Combined moderate and mild atypical sputum classifications were significantly more frequent among the "frequent users" than among the nonpatient controls($p<0.005$) and among the "frequent users" than among the patient controls ($p<0.10$). The absence of any normal sputum samples among the "frequent users" is quite striking and suggests that

some agents used in some pressurized aerosol cans may be carcinogenic and that further exploration be done on aerosol ingredients. Until such studies exonerate pressurized aerosol products, they should be used in ways which minimize aerosol inhalation.

4310 MEASUREMENTS OF VINYL CHLORIDE FROM AEROSOL SPRAYS. (Eng.) Gay, B. W., Jr. (Environmental Protection Agency, Natl. Environmental Res. Center, Res. Triangle Park, N.C. 27711); Lonneman, W. A.; Bridbord, K.; Moran, J. B. *Ann. N.Y. Acad. Sci.* 246:286-295; 1975.

Human exposure levels and the decay of vinyl chloride in home and office environments were studied. Aerosol hair and insect sprays known to contain vinyl chloride were released under conditions simulating actual use conditions in typical home and office environments. Cryogenic trapping concentration procedures were used to collect samples and introduce them into a gas chromatographic system for analysis. Detection of vinyl chloride was by flame ionization. In all experiments, high concentrations of vinyl chloride were detected when the vinyl chloride-containing aerosol sprays were used. A 30-sec release of hairspray in a 56,000-l room produced vinyl chloride in concentrations of 13.10-13.70 ppm two minutes after spray; the concentrations were 0.06-0.10 ppm 360 min after spray. A 60-sec release of hairspray in a 29,300-l room produced concentrations of 122.7-124.4 ppm during the spray, with 0.12-o.13 ppm remaining 120 min later. A 30-sec release of insect spray in a 21,400-l room produced a vinyl chloride concentration of 380.1-383.6 ppm one minute after spray, with a concentration of 0.65-0.83 ppm remaining in an adjacent hall 151 min later. A 120-sec release of insect spray in a 133,000-l room produced an initial concentration of 41.64-41.9 ppm vinyl chloride, with concentration at 120 min of 0.01-0.012 ppm. In all cases, the user was exposed to high peak concentrations, even with good ventilation in the room. When the aerosol spray was released in smaller-sized rooms, higher concentrations of vinyl chloride persisted for some time, the decrease in concentration with time apparently being a dilution effect of room ventilation. Based on these data, predicted past exposures to vinyl chloride resulting from the use of household products were determined; these exposures were substantially above current proposed occupational standards for this substance, especially among women. On this basis, the frequency of angiosarcoma of the liver among the general population may be increased in coming years.

4311 THE VALUE OF PREDICTIVE EXPERIMENTAL BIOASSAYS IN OCCUPATIONAL AND ENVIRONMENTAL CARCINOGENESES. AN EXAMPLE: VINYL CHLORIDE. (Eng.) Maltoni, C. (Istituto di Oncologia "Felice Addarii", Ospedali di Bologna, Ente Ospedaliero Regionale. Viale Ercolani 4/2, 401 38 Bologna, Italy). *Ambio* 4(1):18-23; 1975.

The first completed experiment of a series on the effects of vinyl chloride (VC) indicates that inhalation of VC by Sprague Dawley rats produced: Zymbal gland carcinomas, nephroblastomas, angiosarcomas and angiomas of the liver and other sites, skin carcinomas, hepatomas and brain neuroblastomas. Th percentage of rats with liver angiosarcoma was 15, 22, 7, and 2 (1 of 59 rats) at 10,000; 6,000; 250; and 50 ppm VC respectively. The inhalation exposur was 4 hr/day, 5 days/wk, for 52 wk. Preliminary results obtained with hamsters, mice, Wistar rats, and different routes of administration, are discussed. The tumors correlated with occupational exposure (liver angiosarcomas, brain and lung tumor lymphomas, leukemias) have been produced by VC exposure in rats, mice, and hamsters.

4312 CARCINOGENICITY BIOASSAYS OF VINYL CHLORIDE: CURRENT RESULTS. (Eng.) Maltoni, C. (Inst. Oncol., Bologna, Italy); Lefemin G. *Ann. N.Y. Acad. Sci.* 246:195-218; 1975.

The effects of vinyl chloride (VC) on hamsters, Swi mice, Wistar rats, and Sprague-Dawley rats were investigated. VC was administered by inhalation (50-30,000 ppm, 4 hr/day, 5 days/wk, for up to 12 mo), orally, or by sc or ip injection to newborn, adult, and pregnant animals. The animals were examined at weekly intervals, and were autopsied at death. All animals exposed to 10,000-30,000 ppm VC were also examined radiologically. VC produced tumors in the adults of all species studied. When administered by inhalation, VC produced Zymbal gland carcinomas, nephroblastomas, angiosarcomas, angiomas; skin carcinomas, hepatomas, and brain neuroblastomas in the rats; lung adenomas (frequently undergoing malignant transformation), mammary carcinomas, angiosarcomas, angiomas, and skin epithelial tumors in the mice; and liver angiosarcomas, skin trichoepitheliomas, and lymphomas in the hamsters. Liver angiosarcomas were observed in all three species. The carcinogenic effect of VC was apparent in the inhalation experiments at 50 ppm. For angiosarcomas and nephroblastomas, the carcinogenic effect was dose-dependent. The neoplastic effect also varied according to the length of VC inhalation exposure. Preliminary results suggest that the carcinogenic effect of VC may vary between Wistar and Sprague-Dawley rats. The appearance of two sc angiosarcomas in the offspring of females exposed to VC for seven days during pregnancy also suggests that VC may have a transplacental effect. Finally, a few cases of ossifying angiosarcomas were found among the exposed animals, suggesting a new orientation in the pathogenic interpretation of acroosteolysis in workers exposed to VC.

4313 VINYL CHLORIDE MONOMER: COMMENTS ON ITS HEPATOTOXICITY AND INTERACTION WITH 1,1-DICHLOROETHYLENE. (Eng.) Jaeger, R. J. (Harvard Sch. Public Health, Boston, Mass.). *Ann. N.Y. Acad. Sci.* 246:150-151; 1975.

The hepatotoxicity of vinyl chloride monomer (VCM) and its interaction *in vivo* with 1,1-dichloroethylene (1,1-DCE) are discussed. 1,1-DCE has been shown to be a potent hepatotoxin which, like VCM, is a chlorinated ethene subject to free radical polymerization. Workers at the B.F. Goodrich Louisville polyvinyl chloride facility who developed angio-

sarcoma of the liver were also exposed to 1,1-DCE. In rats, chronic and acute exposure to VCM resulted in a reduction in hepatic glutathione concentrations, whereas acute inhalation exposure produced no elevation in serum alanine-α-ketoglutarate transaminase (AKT) in fed and fasted rats. Acute exposure produced no deaths or CNS depression. Inhalation exposure to 1,1-DCE produced a 50-fold elevation in serum AKT activity; this elevation was prevented by simultaneous exposure to VCM, the protection being concentration-dependent. With respect to the proximate agent responsible for VCM hepatotoxicity, there is evidence that β-chloroethanol is formed as an *in vitro* intermediate. Intramolecular nucleophilic displacement of chlorine by the hydroxyl group on the α-carbon would result in the formation of a positively charged protonated epoxide which would suggest the electrophilicity of alkylating groups as a requirement for tumorigenicity. Such a transformation is unlikely for 1,1-DCE or trichloroethylene. Bonding considerations suggest that other monohalothenes such as vinyl bromide and vinyl iodide may be more tumorigenic than vinyl chloride; this hypothesis should be tested.

4314 HYPERPLASIA OF HAMSTER TRACHEAL EPITHELIUM CAUSED BY AMOSITE ASBESTOS IN ORGAN CULTURE [abstract]. (Eng.) Frank, A. L. (Natl. Cancer Inst., Bethesda, Md. 20014); Sporn, M. B.; Kaufman, D. G. *Proc. Am. Assoc. Cancer Res.* 16:113; 1975.

4315 THE TUMOR-TETANUS ASSAY -- EXPERIMENTAL STUDIES ON THE BIOLOGICAL DIFFERENTIATION BETWEEN CARCINOGENESIS AND ORGAN REGENERATION OF THE RAT. (Ger.) Schneeweiss, U. (Akademie der Wissenschaften der DDR, Zentralinstitut fur Krebsforschung, Robert-Rossle-Klinik, DDR 1115 Berlin-Buch, Lindenberger Weg 80, East Germany); Fabricius, E.-M. *Arch. Geschwulstforsch.* 45(1):3-15; 1975.

4316 EXPERIMENTAL CARCINOGENESIS OF THE LIVER IN THE WHITE RAT PROGENY AFTER ADMINISTRATION ON PARADIMETHYLAMINEAZOBENZOL. (Rus.) Titova, G. N. (Dept. Cytology, Histology and Embryology, Medical Inst. Sanitation and Hygiene, Leningrad, U.S.S.R.). *Arkh. Anat. Gistol. Embriol.* 68(1):98-102; 1975.

4317 FOCI OF ENZYME DEFICIENCY IN RAT LIVER DURING AZO DYE CARCINOGENESIS [abstract]. (Eng.) Murthy, M. S. (Inst. Cancer Montreal, Centre Hospitalier Notre-Dame, Montreal, Canada); Daoust, R. *Proc. Am. Assoc. Cancer Res.* 16:38; 1975.

4318 EXPERIMENTAL STUDY ON CARCINOGENIC ACTIVITY OF PROPANOL-1, 2-METHYLPROPANOL-1 AND 3-METHYLBUTANOL-1. (Ger.) Gibel, W. (Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, 1115 Berlin-Buch, Lindenberger Weg 80, East Germany); Lohs, K.; Wildner, G. P. *Arch. Geschwulstforsch.* 45(1):19-24; 1975.

4319 INDUCTION OF CHROMOSOME DAMAGE IN FIBROBLASTS FROM GENETIC INSTABILITY SYNDROMES [abstract]. (Eng.) Wolman, S. R. (New York Univ. Sch. Medicine, New York, N.Y. 10016); Auerbach, A. D. *Proc. Am. Assoc. Cancer Res.* 16:69; 1975.

4320 ALTERED REGULATION OF α-AMINOLEVULINIC ACID SYNTHETASE (ALAS) IN ETHIONINE CARCINOGENESIS [abstract]. (Eng.) Woods, J. S. (Natl. Inst. Environ. Health Sci., Res. Triangle Park, N.C. 27709). *Proc. Am. Assoc. Cancer Res.* 16:40; 1975.

4321 THE REACTION OF ^{14}C-LABELLED BIS-(CHLOROMETHYL) ETHER WITH DNA [abstract]. (Eng.) Goldschmidt, B. M. (New York Univ. Medical Center, New York, N.Y. 10016); Van Duuren, B. L.; Frenkel, K. *Proc. Am. Assoc. Cancer Res.* 16:66; 1975.

4322 A SYNERGISTIC EFFECT OF ULTRAVIOLET LIGHT AND ETHIDIUM BROMIDE ON PETITE INDUCTION IN YEAST. (Eng.) Hixon, S. C. (Fondation Curie, Inst. du Radium, Batiment 110, F-91405 Orsay, France); Yielding, K. L. *Mutat. Res.* 29(1):159-163; 1975.

4323 INHIBITION OF DNA DEGRADATION BY BOUND 2-ACETAMIDOFLUORENE [abstract]. (Eng.) Scribner, J. D. (Fred Hutchinson Cancer Res. Center, Seattle, Wash. 98104); Naimy, N. K. *Proc. Am. Assoc. Cancer Res.* 16:65; 1975.

4324 ENZYMES INVOLVED IN MUTAGEN FORMATION FROM 2-ACETYLAMINOFLUORENE [abstract]. (Eng.) Shaw, C. R. (M.D. Anderson Hosp. and Tumor Inst., Houston, Tex. 77025); Stout, D. L.; Baptist, J. N. *Proc. Am. Assoc. Cancer Res.* 16:199; 1975.

4325 ALTERATION OF DEOXYRIBONUCLEIC ACID TRANSFORMING ACTIVITY IN *BACILLUS SUBTILIS* BY N(OH)-AMINOACETYLFLUORENE [abstract]. (Eng.) Felkner, I. C. (Univ. Texas System Cancer Center and Health Science Center, Houston, Tex. 77025); Matney, T. S.; Shaw, C. R.; Hickey, R. C. *Proc. Am. Assoc. Cancer Res.* 16:200; 1975.

4326 CARCINOGENESIS BY LOCAL APPLICATION OF FLUORENYLHYDROXAMIC ACIDS TO THE MAMMARY GLAND OF THE RAT [abstract]. (Eng.) Malejka-Giganti, D. (VA Hosp., Minneapolis, Minn. 55417); Gutmann, H. R.; Rydell, R. E. *Proc. Am. Assoc. Cancer Res.* 16:62; 1975.

4327 CATECHOLAMINES IN URINE AND TUMOR TISSUE IN CASES OF UNI- AND BILATERAL PHEOCHROMOCYTOMA. (Ger.) Poch, G. (Institut fur experimentelle und klinische Pharmakologie, Graz, Austria); Kukovetz, W. R.; Becker, H.; Cesnik, H. *Med. Klin.* 70(5):190-196; 1975.

4328 TUMORIGENICITY OF *n* PROPYL-, *n* AMYL- AND *n* ALLYL-HYDRAZINES. TOXICITY OF AGARITINE [abstract]. (Eng.) Toth, B. (Univ. Nebraska Medical Center, Omaha, Nebr. 68105); Nagel, D.; Shimizu, H.; Sornson, H.; Issenberg, P.; Erickson, J. *Proc. Am. Assoc. Cancer Res.* 16:61; 1975.

4329 ALTERATIONS IN HEPATIC POLYAMINE LEVELS IN RATS FOLLOWING HYDRAZINE TREATMENT [abstract]. (Eng.) Banks, W. L., Jr. (Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, Va. 23298); Hubbard, V. S. *Proc. Am. Assoc. Cancer Res.* 16:110; 1975.

4330 GROWTH RATE OF 1,2 DIMETHYL-HYDRAZINE INDUCED COLON ADENOCARCINOMA IN RAT [abstract]. (Eng.) Maskens, A. P. (Univ. Louvain, Louvain Sch. Medicine, Louvain, Belgium); Meersseman, F. P.; Rahier, J. *Proc. Am. Assoc. Cancer Res.* 16:17; 1975.

4331 CHROMOSOME ANALYSES AFTER PROPHYLACTIC AND THERAPEUTIC APPLICATION OF INH IN MAN. [abstract]. Obe, G. (Genetisches Inst. der FU, Berlin, West Germany); Beek, B.; Gebhart, E.; Fonatsch, C.; Bauchinger, M.; Schmid, E. *Mutat. Res.* 29(2):257-258; 1975.

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4334 THE EFFECT OF UNSATURATED FATTY ACIDS ON CARCINOGENIC ACTIVITY OF OVERHEATED SUNFLOWER OIL. (Rus.) Vysheslavova, M. Ia. (Inst. Nutr. U.S.S.R. Acad. Med. Sci., Moscow); Kozlova, I. N. *Vopr. Onkol.* 21(4):40-44; 1975.

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4344 MUTATIONS IN PLANTS, MICROORGANISMS AND IN HOST-MEDIATED ASSAY SYSTEMS. MUTAGENICITY STUDIES IN MICROORGANISMS *IN VITRO*, WITH EXTRACTS OF MAMMALIAN ORGANS, AND WITH THE HOST-MEDIATED ASSAY. (Eng.) Mohn, G. (Zentrallaboratorium fur Mutagenitatsprufung der DFG, Freiburg, West Germany); Ellenberger, J.; McGregor, D.; Merker, H.-J. *Mutat. Res.* 29(2):221-233; 1975.

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4348 CHANGE IN CARCINOGENIC POTENCY OF NITROSAMINES BY SUBSTITUTION [abstract] (Eng.) Lijinsky, W. (Carcinogenesis Program, Biology Div., ORNL, Oak Ridge, Tenn. 37830); Taylor, H. W. *Proc. Am. Assoc. Cancer Res.* 16:61; 1975.

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4350 METHYL(ACETOXYMETHYL)NITROSAMINE: A NEW CARCINOGEN HIGHLY SPECIFIC FOR COLON AND SMALL INTESTINE [abstract]. (Eng.) Rice, J. M. (Natl. Cancer Inst., Bethesda, Md. 20014); Joshi, S. R.; Roller, P. P.; Wenk, M. L. *Proc. Am. Assoc. Cancer Res.* 16:32; 1975.

4351 EFFECTS OF UNILATERAL NEPHRECTOMY ON DEVELOPMENT OF KIDNEY TUMORS IN RATS TREATED WITH DIMETHYLNITROSAMINE AND BASIC LEAD ACETATE. (Jpn.) Yoshida, K. (Nara Medical Univ., Nara, Japan). *Hinyokika Kiyo* 21(1):31-38; 1975.

4352 THE MICROBIOLOGICAL EFFECTS OF NITRATE AND NITRITE [abstract]. (Eng.) Roberts, T. A. (ARC Meat Res. Inst., Langford, Bristol BS18 7DY, England). *J. Sci. Food Agric.* 26(3):380-381; 1975.

4353 THE ANALYSIS OF NITRATE AND NITRITE IN FOODSTUFFS: A CRITICAL REVIEW [abstract]. (Eng.) Usher, C. D. (Unilever Res. Lab. Colworth/Welwyn, Colworth House, Sharnbrook, Beds, U.K.); Telling, G. M. *J. Sci. Food Agric.* 26(3):384; 1975.

4354 STUDIES OF A NITROSOBUTYLUREA INDUCED W/FU RAT GRANULOCYTIC LEUKEMIA(GL) MODEL OF HUMAN LEUKEMIA [abstract]. (Eng.) Okada, K. (Res. Inst. for Nuclear Medicine and Biology, Hiroshima, Japan); Teratani, M.; Takahashi, A.; Uchino, H. *Proc. Am. Assoc. Cancer Res.* 16:203; 1975.

4355 EARLY NEOPLASTIC EVENTS IN TRANSPLACENTAL CARCINOGENESIS [abstract]. (Eng.) Swenberg, J. A. (Ohio State Univ., Columbus, Ohio 43210); Clendenon, N.; Denlinger, R.; Gordon, W. *Proc. Am. Assoc. Cancer Res.* 16:63; 1975.

4356 CARCINOGENIC ACTION OF QUINOXALINE 1,4-DIOXIDE IN RATS. (Eng.) Tucker, M. J. (Pharm. Div., Imp. Chem. Ind. Ltd., Macclesfield, England). *J. Natl. Cancer Inst.* 55(1):137-146; 1975.

4357 INDUCTION OF ORNITHINE DECARBOXYLASE AND S-ADENOSYL-L-METHIONINE DECARBOXYLASE IN MOUSE EPIDERMIS BY TUMOR PROMOTERS [abstract]. (Eng.) O'Brien, T. G. (McArdle Lab., Univ. Wisconsin, Madison, Wis. 53706); Boutwell, R. K. *Proc. Am. Assoc. Cancer Res.* 16:62; 1975.

4358 STIMULATED DNA SYNTHESIS IN MOUSE EPIDERMAL CELL CULTURES TREATED WITH 12-O-TETRADECANOYL PHORBOL-13-ACETATE [abstract]. (Eng.) Yuspa, S. H. (Natl. Cancer Inst., Bethesda, Md. 20014); Hennings, H.; Ben, T. *Proc. Am. Assoc. Cancer Res.* 16:69; 1975.

4359 MUTAGENIC EFFECT OF THIO-TEPA ON LABORATORY MICE. IV. EFFECT OF THE GENOTYPE AND SEX ON THE RATE OF CHROMOSOME ABERRATIONS IN BONE MARROW CELLS. (Rus.) Surkova, N. I. (Res. Lab. of Experimental-Biological Models, Acad. Medical Sciences of U.S.S.R., Moscow Region, U.S.S.R.); Malashenko, A. M. *Genetika* 11(1):61-72; 1975.

4360 MUTAGENICITY OF VINYL CHLORIDE AND DERIVATIVES IN *S. TYPHIMURIUM* STRAINS [abstract]. (Eng.) Bartsch, H. (International Agency for Research on Cancer, 69008 Lyon, France); Malaveille, C.; Montesano, R.; Croisy, A.; Jacquignon, P. *Proc. Am. Assoc. Cancer Res.* 16:22; 1975.

4361 PROPERTIES OF ACIDIC SACCHARIDES PRODUCED BY B16 MELANOMA CELLS TREATED WITH 1-METHYL-3-ISOBUTYLXANTHINE. (Eng.) Banks, J. (Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, Pa. 17033); Kreider, J. W.; Satoh, C.; Davidson*, E. A. *Cancer Res.* 35(9):2383-2389; 1975.

See also:

* (Rev): 4201, 4204, 4203, 4204, 4205, 4206 4230, 4231, 4232, 4233, 4234, 4236, 4237, 4262
* (Phys): 4363, 4367, 4368, 4370
* (Immun): 4435, 4437, 4493, 4495, 4501, 4512, 4532, 4533, 4544, 4546
* (Path): 4556, 4567, 4572, 4599, 4607, 4624
* (Epid-Biom): 4657, 4663, 4664, 4665, 4667, 4673, 4676, 4677, 4678

4362 CELLULAR INJURY AND CELL PROLIFERATION IN SKIN CARCINOGENESIS BY UV LIGHT. (Eng.) Stenback, F. (Univ. Nebraska Medical Center, Omaha, Nebr. 68105). *Oncology* 31(2):61-75; 1975.

The effects on mouse skin of varying doses of light from a high-voltage mercury lamp were compared to the alterations occurring after repeated light applications from a carbon-arc xenon sunlamp. Skin samples were taken immediately before, immediately after, and at intervals ranging from 30 min to 30 days after irradiation. A single dose of UV light at a carcinogenic wavelength (5.5×10^7 erg/cm^2) caused necrosis and ulceration, followed by scarring, but failed to produce tumors. In the case of three small doses (1.5×10^8 erg/cm^2), the neoplastic response was predominantly epithelial, resulting in formation of papillomas and squamous cell carcinomas. Increasing the dose (2.75×10^8 erg/cm^2, five doses; or 3.9×10^9 erg/cm^2, 20 doses) caused formation of fibromas and fibrosarcomas of the ear. However, repeated application of UV light having a spectrum similar to sunlight failed to induce tumors. In these studies, only animals showing initially destructive lesions ultimately presented tumor formation, while the hyperplasia induced by UV irradiation showed no relationship to neoplastic transformation. The results emphasize the significance of dose and wavelength in evaluating effects of UV-light skin carcinogenesis.

4363 ULTRAVIOLET LIGHT IRRADIATION AS INITIATING AGENT IN SKIN TUMOR FORMATION BY THE TWO-STAGE METHOD. (Eng.) Stenback, F. (Dept. Pathol., Univ. Oulu, Finland). *Eur. J. Cancer* 11(4):241-246; 1975.

The biological and morphological characteristics of neoplastic progression in Swiss mouse skin induced by the two-stage method, using UV light as an initiator and croton oil as a promoter, were studied by biological and histological methods. UV light (5.5×10^7 erg/cm^2) proved to be an effective initiator in skin tumor formation, when followed by repeated applications of croton oil. In comparison with experiments using 7,12-dimethylbenz(a)anthracene (50 µg) as an initiator, the average latent period was longer and the number of tumor-bearing animals and of tumors was lower. Morphologically, an orderly epidermal hyperplasia, progressing through papillomatous hyperplasia and ending in extroverted squamous cell papillomas, occurred in only a few animals. The proliferation of epithelial cells induced by multiple UV irradiation was disorderly with distinct cytological and histological abnormalities. A few squamous cell carcinomas developed from the borders of ulcers induced by repeated UV light applications. Efforts to increase the neoplastic response, by giving either UV light ten times prior to promotion or croton oil immediately after each of 16 UV irradiations, did not increase the total number of tumors but did induce some malignant ones. These studies emphasize the specificity of initiation and promotion in skin tumor formation and the different actions of physical and chemical carcinogens on animal skin, depending upon the combination of progression and persistence of destructi and proliferative actions specific to each agent.

4364 THE RISK OF TUMOR INDUCTION IN MAN FOLLOWING MEDICAL IRRADIATION FOR MALIGNANT NEOPLASM. *(Eng.)* Seydel, H. G. (American Oncologic Hosp. of the Fox Chase Cancer Center, Central and Shelmire Aves., Philadelphia, Pa. 19111). *Cancer* 35(6):1641-1645; 1975.

The possible carcinogenic effects of therapeutic irradiation for malignancy were assessed. A review of second malignant tumors (SMT) from the joint tumor regristry of the Fox Chase center was carried out. Cases entered between 1929 and 1973 for primary sites in the cervix, oral cavity, and oropharynx were analyzed. The number of five-year survivors was determined and the incidence of SMT was expressed as a percentage. Three patients developed adenocarcinoma of the endometrium in a uterus which had been previously irradiated for squamous cell carcinoma of the cervix. The average dose was 8100 rads. There were 354 five-year survivors among the 933 patients treated for cancer. SMT in the form of adenocarcinoma of the endometrium occurred in 0.85% of the five-year survivors. Nine SMT of the oropharynx and the oral cavity occurred in the irradiated mucosa of 611 five-year survivors among 1464 patients treated by radiotherapy. The average dose was 6800 rads. SMT occurred in 1.14% of the five-year survivors. Review of the tumor registry revealed 407 patients who were treated surgically for cancers of the oral cavity or oropharynx SMT in the upper respiratory and digestive tract occurred in 8 (2%). SMT of this region following radiotherapeutic treatment, including lesions outside the irradiated area, was 23 among 1464 patients (1.6%).

4365 FUNCTION OF THE UVR MARKER IN DARK REPAIR OF DNA MOLECULES. *(Eng.)* Sedliakova, M. (Cancer Res. Inst., Slovak Acad. Sciences, 880 32 Bratislava, Czechoslovakia); Brozmanova, J.; Slezarikova, V.; Masek, F.; Fandlova E. *Neoplasma* 22(4):361-384; 1975.

The function of the *uvr* marker in dark repair of DNA molecules was investigated in cultures of *Escherichia coli* K12 and *E. coli* 15T$^-$, both strains of the *uvr*$^+$ *rec*$^+$ genotype, and in an *E. coli* K12 *rec*$^+$ *uvr*$^-$ culture. Cell suspensions were irradiated (254 nm radiation, 6.3 ergs/mm/sec) in a 1-2 mm thick layer with continuous stirring. DNA was labeled with [^{3}H]thymidine for various periods after irradiation. In some experiments, the cultures were pretreated to produce amino acid and thymine starvation, amino acid starvation only, or thymine starvation only. Thymine dimers were determined radiochromatographically in the fraction precipitated in trichloroacetic acid. Molecular weight of NDA was estimated from alkaline sucrose gradient sedimentation profiles. Combined amino acid and thymine prestarvation resulted in depression of dimer excision in both *E. coli* strains of the *uvr*$^+$ genotype. Depression of excision, however, was

without influence on the sedimentation profile of DNA daughter chains. A comparison of the effectiveness of repair of daughter chains synthesized after irradiation in K12 *uvr*$^+$ and *uvr*$^-$ cells indicated that the *uvr*$^+$ cells are able to tolerate a much higher amount of unexcised dimers. To determine the connection between the capacity of cells to tolerate unexcised dimers and their ability to restore DNA daughter chains, the sedimentation profiles of DNA labeled at different intervals after irradiation were compared. The size of the DNA chains in the treated *uvr*$^+$ cells (irradiation with a dose of 750 ergs and two-hr postincubation) did not differ from the chains of the unirradiated sample indicating that the postreplication repair mechanism was effective enough to secure a successful repair of at least 50% of the induced dimers which had persisted in the treated cells. The *uvr*$^-$ strain was apparently lacking such an effective mechanism. It is suggested that the *uvr* loci are involved not only in excision but also control an efficient restoration mechanism operating at the level of DNA chains synthesized after UV irradiation. It is further suggested that the mechanism probably involves that part of the enzymatic potential which is necessary for cells to carry on excision.

4366 RADIATION-INDUCED DIVISION DELAY IN CHO CELLS: REPAIR KINETICS. *(Eng.)* Leeper, D. B. (Thomas Jefferson Univ. Hosp., Philadelphia, Pa.). *Cell Cycle in Malig. Immun., Proc. Annu. Hanford Biol. Symp., 13th.* Richland, Washington, D. C., U.S. Energy Research and Development Administration, 1975, pp. 193-210.

The kinetics of the recovery from radiation damage manifest as division delay was analyzed in Chinese hamster ovary fibroblasts in monolayer culture using two-dose fractionation schemes and suboptimal postirradiation temperatures in a manner similar to the analysis of the repair of sublethal and potentially lethal radiation damage. Mitotic-cell selection was used to assess the rate of cell division. Fractionation of a single dose of 300 rads into two 150-rad fractions separated by intervals of time and analysis of the division delay remaining at the time of the second dose showed that the damage resulting in division delay is repaired at a constant rate of one minute of delay per minute between dose fractions. However, when a 600-rad single dose was fractionated into two 300-rad fractions, a bimodal-recovery pattern resulted. After a dose of 300 rads, damage manifest as division delay was repaired initially (up to 0.4 hr postirradiation) by a rapid recovery process at the rate of 3.6 min of delay per minute between dose fractions, after which a second and slower recovery process became operant, with damage being repaired at the rate of 0.55 min of delay per minute between dose fractions. Lowering the postirradiation incubation temperature to 4, 20, or 30 C or lowering the temperature between two-dose fractions reduced the rate of recovery. The construction of an Arrhenius plot showed that the repair process was enzymatic with an activation energy of 11,000 cal/M and a Q_{10} of 1.82. Neither fractionation nor postirradiation treatment with suboptimal incubation temperatures modified the recovery from division delay in a way that resembled the recovery from sublethal or potentially lethal radiation damage. This provides further evidence that the respective radiosensitive targets are distinct.

4367 EXPERIMENTAL MODIFICATION OF PHOTOCARCINOGENESIS. II. FLUORESCENT WHITENING AGENTS AND SIMULATED SOLAR UVR. (Eng.) Forbes, P. D. (Temple Univ. Health Sci. Cent., Philadelphia, Pa.); Urbach, F. *Food Cosmet. Toxicol.* 13(3):339-342; 1975.

4368 EXPERIMENTAL MODIFICATION OF PHOTOCARCINOGENESIS. III. SIMULATION OF EXPOSURE TO SUNLIGHT AND FLUORESCENT WHITENING AGENTS. (Eng.) Forbes, P. D. (Temple Univ. Health Sci. Cent., Philadelphia, Pa.); Urbach, F. *Food Cosmet. Toxicol.* 13(3):343-345; 1975.

4369 POTENTIAL GENETIC EFFECTS OF PHOTOTHERAPY FOR NEONATAL JAUNDICE [abstract]. (Eng.) Speck, W. T. (Dept. Pediatr., Columbia Univ., New York, N.Y.); Rosenkranz, H. S. *Proc. Am. Assoc. Cancer Res.* 16:16; 1975.

4370 PHOTOTOXICITY AND PHOTOCARCINOGENESIS: COMPARATIVE EFFECTS OF ANTHRACENE AND 8-METHOXYPSORALEN IN THE SKIN OF MICE [abstract]. (Eng.) Forbes, P. D. (Temple Univ. Health Sci. Cent., Philadelphia, Pa.); Davies, R. E.; Urbach, F. *Proc. Am. Assoc. Cancer Res.* 16:120; 1975.

4371 MULTIPLE FLUOROSCOPY OF THE CHEST: CARCINOGENICITY FOR THE FEMALE BREAST AND IMPLICATIONS FOR BREAST CANCER SCREENING PROGRAMS. (Eng.) Delarue, N. C. (Suite 530, 170 St. George St., Toronto, Ont. M5R 2M8, Canada); Gale, G.; Ronald, A. *Can. Med. Assoc. J.* 112(12):1405-1412; 1975.

4372 CANCER OCCURRENCE AFTER REPEATED FLUOROSCOPY DURING PNEUMOTHORAX THERAPY [abstract]. (Eng.) Uzman, B. G. (Veterans Administration Hosp., Shreveport, La.). *IRCS Med. Sci.* 3(10/Suppl.):23; 1975.

See also:

* (Rev): 4207, 4208, 4209, 4235, 4237, 4260
* (Chem): 4322, 4339
* (Immun): 4438, 4439, 4511
* (Path): 4610, 4635
* (Epid-Biom): 4653, 4662, 4675, 4680

4373 GENERATION OF AVIAN MYELOBLASTOSIS VIRUS STRUCTURAL PROTEINS BY PROTEOLYTIC CLEAVAGE OF A PRECURSOR POLYPEPTIDE. (Eng.) Vogt, V. M. (Inst. General Microbiology, Univ. Bern, Altenbergrain 21, 3013 Bern, Switzerland); Eisenman, R.; Diggelmann, H. *J. Mol. Biol.* 96(3):471-493; 1975.

A cleavage pathway for the generation of the structural proteins of avian myeloblastosis virus (AMV) was studied. AMV-infected primary chick fibroblasts were pulse-labeled with [^{35}S]methionine, incubated, and then lysed with cold lysis buffer. Cytoplasmic fractions were prepared by centrifugation of the lysates; to the supernatant from each plate of cells, 2-5 μg of AMV and 0.1 ml of rabbit anti-AMV serum were added. The immune precipitate was collected by centrifugation and was analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and agarose gel filtration. Gel electrophoresis of the immune precipitates of the labeled cells revealed five metabolically unstable radioactive proteins (pr12, pr32, pr60, pr66 and pr76). Double-labeled ion-exchange chromatography of the tryptic digests of these polypeptides demonstrated that the largest precursor, pr76, contained the amino acid sequences of all four of the internal structural proteins that bear the group-specific antigenic determinants of the virus (p28, p17, p10, and p14). Pr76 appeared not to contain the sequence of the fifth and smallest internal virion protein (p7). The four smaller precursors were intermediate cleavage products of pr76. The arrangement of the virion proteins in pr76 was determined by labeling the cells shortly after inhibiting polypeptide chain initiation. The relative amounts of radioactivity in both the completed virion proteins and the tryptic peptides of pr76 implied the same order for 3 of the 4 proteins, although the exact position of one protein remains uncertain. The cleavage of percursors proceeded in crude extracts of AMV-infected cells. Thus, proteolysis was resistant to several protease inhibitors, but was completely blocked by the addition of agents that disrupt membranes. It is suggested that the processing of pr76 begins by removal of a C-terminal fragment, which in turn is trimmed to yield virion p14. The larger polypeptide remaining after the first cleavage ultimately forms virion proteins p28, p17, and p10. It is likely that the precursors are attached to and cleaved on the cell membrane.

4374 SYNTHESIS AND FUNCTION OF AVIAN SARCOMA VIRUS-SPECIFIC DNA IN PERMISSIVE AND NONPERMISSIVE HOST CELLS. *(Eng.)* Varmus, H. E. (Dept. Microbiology, Univ. California, San Francisco, Calif.); Guntaka, R. V.; Deng, C. T.; Domenik, C.; Bishop, J. M. *Proc. Int. Cancer Congr. 11th.* Vol. 2 (*Chemical and Viral Oncogenesis*). Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 272-277.

Recent attempts to describe the mechanism(s) by which RNA tumor virus genes are synthesized, inserted into the DNA of the host cell, and subsequently transcribed into viral DNA are summarized. The experiments were performed with several strains of avian sarcoma virus, principally B77 virus, and the intermediates to viral replication were monitored with nucleic acid hybridization. During the first six hours after infection of duck cells by B virus, virus-specific DNA was detectable in cytoplasmic but not in nuclear fractions. Viral DNA was also produced in normal amounts in chemically enucleated duck cells. During synthesis in the cy plasm, the viral DNA was associated with particles which pelleted at 100,000 *g* and banded at 1.16 in equilibrium sucrose gradients. Between 6 and 9 hr after infection, the viral DNA migrated to the nucleus and first became integrated into the host genome. Integration was compared within 24-48 hr, transcription of new viral RNA was apparent 14-18 hr postinfection, and the level of viral RNA and the release of mature viral particles increased for at least three days. Fully transformed cultur of duck cells contained 4-6 copies of viral DNA an several thousand equivalents of viral RNA. The synthesis of viral DNA in infected cells was catalyzed by the virus-coded RNA-directed DNA polymera associated with the mature virus particle. Ethidi bromide, a phenanthidine dye which intercalates in DNA, markedly depressed the integration of avian sarcoma viral DNA without appreciably affecting it rate of synthesis. There is evidence to indicate that ethidium bromide inhibits integration by preventing or reversing the formation of closed circu DNA. Other results indicate that viral DNA may be made in the following sequence: complete copying of the RNA genomic subunit into a strand of DNA; nicking of the viral RNA, which may then serve as a primer for the synthesis of short pieces of "plu strand; concomitant digestion of the viral RNA; ligation of the "plus" strand segments; and formatio of a closed circle.

4375 STRAIN SPECIFICITY OF CHANGES IN ADENYLA CYCLASE ACTIVITIY IN CELLS TRANSFORMED B AVIAN SARCOMA VIRUSES. (Eng.) Yoshida, M. (Fac. Pharm. Sci., Univ. Tokyo, Japan); Owada, M.; Toyoshima, K. *Virology* 63(1):68-76; 1975.

The relationship between viral functions and chang in enzyme activities was examined by measuring the adenylate cyclase and cyclic AMP phosphodiesterase activities in chick embryo fibroblasts transformed by the avian sarcoma virus B77, the Prague and Schmidt-Ruppin strains of Rous sarcoma virus, and their temperature sensitive mutants. Infected chi embryo fibroblasts were transferred once before tests to induce extensive transformation of culture cells. Enzyme activity was determined by paper chromatography of cell homogenates. With both normal chick embryo fibroblasts and transformed cells, adenylate cyclase activity was linear for at least ten minutes and phosphodiesterase was linear for more than 30 min at 37 C. The transformed chick embryo fibroblasts had lower activities of adenylat cyclase, but they had the same activity of cyclic AMP phosphodiesterase as control cells. The cells infected with their temperature-sensitive mutants i the transforming capacity also had reduced cyclase activity when grown at the permissive temperature 36 C but normal activity when grown at the nonpermissive temperature 41 C, indicating a close correl

ation between viral transformation and cellular adenylate cyclase activity. The dependencies of adenylate cyclase activity on ATP concentration in normal and transformed cells with 10 mM $MgCl_2$ were compared, and the extent of stimulation of the activity by NaF was also measured. The K_m value for ATP, Mg^{++} dependency, and sensitivity to NaF of the adenylate cyclase activity reduced by viral transformation varied with the viral strain. The enzyme of B77-transformed cells at 41 C had a higher K_m for ATP (0.29 mM) than that of normal cells (0.14 mM). Transformation by the Prague or Schmidt-Ruppin strains of Rous sarcoma virus had no effect on the K_m value of adenylate cyclase for ATP. None of the virus strains induced significant change in the Mg^{++} concentration dependence of the cellular cyclase activity. NaF stimulated the adenylate cyclase activity of normal cells 4- to 8-fold. NaF (10 mM) stimulated the cyclase activity of cells transformed by B77 or the Prague strain of Rous sarcoma virus as much as that of normal fibroblasts, but caused more stimulation in cells transformed with the Schmidt-Ruppin strain of Rous sarcoma virus than in normal fibroblasts. It is concluded that the changes in enzyme activity on transformation are specific to the virus strain and are not related to the virus subgroup.

4376 LOW ONCOGENIC POTENTIAL OF AVIAN ENDOGENOUS RNA TUMOR VIRUS INFECTION OR EXPRESSION. (Eng.) Motta, J. V. (Regional Poultry Res. Lab., East Lansing, Mich. 48823); Crittenden, L. B.; Purchase, H. G.; Stone, H. A.; Witter, R. L. *J. Natl. Cancer Inst.* 55(3):685-689; 1975.

Studies were undertaken to evaluate the potential of endogenous and exogenous Rous-associated virus, type 0 (RAV-) infection for the induction of lymphoid leukosis (LL), the most common chicken neoplasm associated with the leukosis-sarcoma virus group. None of 128 chickens spontaneously releasing RAV-0 and only one of 42 exogenously infected *in ovo* with the virus (5×10^5 infectious U) died with LL. Because the chickens were not kept in strict isolation, it could not be assumed that the one LL was induced by RAV-0. In contrast, RAV-1 infected chickens from the same lines had a high incidence of LL and other neoplasms including sarcomas, nephroblastomas, hemangiomas, and erythroblastosis. Mortality from LL following iv injection of RAV-1 (5×10^2 infectious U) was 21.2% in chicks (52) with endogenous RAV-0 infection, 33.3% in chicks (12) inoculated with RAV-0, and 30.8% in chicks (13) with contact exposure to the virus. Over 800 chicks of several inbred lines were maintained in plastic isolators free of exogenous avian leukosis-sarcoma virus infection for from 500 to nearly 1000 days of age. No LL was observed, even though some lines are known to produce RAV-0 spontaneously or to express inherited group-specific antigen. Three neoplasms of unknown etiology were observed, but none generally associated with leukemia virus infection. It is concluded that avian endogenous virus infection has little, if any, oncogenic potential, and that exogenous avian leukosis viruses are responsible for most naturally occurring neoplasms.

4377 QUANTITATION OF AVIAN RNA TUMOR VIRUS REVERSE TRANSCRIPTASE BY RADIOIMMUNOASSAY. (Eng.) Panet, A. (Hadassah Medical Sch., Jerusalem, Israel); Baltimore, D.; Hanafusa, T. *J. Virol.* 16(1):146-152; 1975.

A radioimmunoassay (RIA) that can detect and quantitate 3-5 ng. of the avian RNA tumor virus reverse transcriptase is described. Avian myeloblastosis virus (AMV, strain A) reverse transcriptase was purified by chromatography on DEAE-Sephadex and phosphocellulose columns; the preparation consisted of two subunits, α and β. The purified enzyme was treated with $Na^{125}I$, and the RIA was carried out using rat anti-AMW reverse transcriptase serum. DNA polymerase activity was also assayed. With high antiserum concentrations, 87% of the iodinated reverse transcriptase was precipitated. The assay detected no antigenic sites in Rous sarcoma virus α virions or in virions of a murine RNA tumor virus (Moloney murine leukemia virus). About 70 molecules of reverse transcriptase were found per AMV virion using either this assay or an assay based on antibody inhibition of enzymatic activity; the RIA indicated that about 3.5% of the virion proteins were reverse transcriptase. The RIA detected about 270 ng of enzyme per milligram of cell protein in virus-producing cells; whereas uninfected cells contained much less antigenic materials, they contained some determinants able to displace radiolabeled antigen. No additional antigenic determinants on reverse transcriptase could be detected that were not found on the α subunit. The RIA was 7-fold less sensitive than the enzymatic assay of DNA polymerase for purified enzyme and 9-fold less sensitive for disrupted virions. However, the RIA is useful in that it can detect antigen using small amounts of protein and in the presence of inhibitors.

4378 ANIMAL DEPENDENT RNA POLYMERASES: PARTIAL PURIFICATION AND PROPERTIES OF THREE CLASSES OF RNA POLYMERASES FROM UNINFECTED AND ADENOVIRUS-INFECTED HeLa CELLS. (Eng.) Hossenlopp, P. (Institut de Chimie Biologique, Faculte de Medecine de Strasbourg, 11 Rue Humann, F-67085 Strasbourg-Cedex, France); Wells, D.; Chambon, P. *Eur. J. Biochem.* 58(1):237-251; 1975.

The class A, B, and C DNA-dependent RNA polymerases from uninfected and adenovirus 2-infected HeLa cells were partially purified and characterized. The enzymes were solubilized, and multiple peaks of enzyme activity were separated by DEAE-Sephadex chromatography. Aliquots of the DEAE-Sephadex peaks were then precipitated with ammonium sulfate and subjected to glycerol density gradient ultracentrifugation. In addition to the class A and B enzyme activities (insensitive and sensitive to inhibition by 10 mM α-amanitin, respectively), three peaks of class C enzyme activity were found that were sensitive to inhibition by 0.1 mM α-amanitin. Rechromatography of these class C peaks indicated that they were not chromatographic artifacts. The class C enzymes differed from the class A and B enzymes not only in their sensitivity to α-amanitin, but in the immunological properties and their ability to transcribe native calf thymus DNA at high ionic strength. How-

ever, the ionic strength optimum and the divalent cation requirements of the class C enzymes were markedly dependent on the nature and the amount of template in the reaction. The multiple enzymes isolated from the infected and uninfected cells showed neither qualitative nor quantitative differences. All of the partially purified HeLa cell RNA polymerases were able to transcribe an intact double-stranded adenovirus 2 DNA under conditions where no transcription occurred with purified calf thymus A1 and B RNA polymerases. Since the multiple enzymes were devoid of endonuclease and exonuclease activities, the ability of the partially purified enzymes to transcribe adenovirus 2 DNA could not be ascribed to the initiation of RNA synthesis at nicks of single-stranded regions of the DNA. No differences in transcriptional ability were found between corresponding enzyme classes from normal and infected cells, but a comparison of the ability of the various enzyme classes to transcribe intact viral DNA revealed large differences. Although partially purified HeLa class A and B enzymes were able to initiate on the intact viral DNA only to a limited extent, the class C enzymes transcribed intact duplex DNA more efficiently than any other class of eukaryotic polymerase yet reported.

4379 ISOLATION AND CHARACTERIZATION OF ADENOVIRUS TYPE 12 DNA BINDING PROTEINS. (Eng.) Rosenwirth, B. (Inst. Virology, Univ. Cologne, Cologne, Germany); Shiroki, K.; Levine, A. J.; Shimojo, H. *Virology* 67(1):14-23; 1975.

The isolation of a set of single strand-specific DNA binding proteins from adenovirus type 12-infected African green monkey kidney (AGMK) cells is described, and the binding proteins are characterized. The proteins were labeled with [^{3}H]leucine, [^{14}C]leucine, or [^{35}S]methionine, after which the cell extract was centrifuged and the supernatant containing the DNA binding proteins was applied to a DNA-cellulose column containing single-stranded calf thymus DNA. The binding proteins thus eluted were dialyzed against buffer and added to single- or double-stranded type 12 adenovirus DNA. The DNA binding proteins were also subjected to sodium dodecyl sulfate-gel electrophoresis and autoradiography. Infection of the AGMK cells with adenovirus type 12 resulted in the production of two single-stranded specific DNA binding proteins of molecular weight 60,000 and 48,000, respectively. Both proteins were synthesized in the absence of viral DNA replication and neither protein appeared to correspond to any polypeptide detected in mature adenovirus virions. Temperature-sensitive mutants from three different early, DNA-negative complementation groups (tsA, tsB, and tsC) were also tested for the production of these proteins at the permissive and nonpermissive temperatures. Mutants of the tsB and tsC classes produced both proteins at 32 and 40 C, while the tsA mutants produced both proteins at 32 C but neither protein at 40 C. The results suggest that the adenovirus type 12 tsA gene induces or codes for the DNA binding proteins, and that adenoviruses in general produce a single strand-specific DNA binding protein that is required for viral DNA replication.

4380 MURINE XENOTROPIC TYPE C VIRUSES: I. DISTRIBUTION AND FURTHER CHARACTERIZATION OF THE VIRUS IN NZB MICE. (Eng.) Levy, J. A. (Dept. Medicine, Univ. California, San Francisco, Calif. 94143); Kazan, P.; Varnier, O.; Kleiman, H. *J. Virol* 16(4):844-853; 1975.

The distribution and properties of NZB-MuLV, an X-tropic murine leukemia virus (MuLV) found in all embryonic and adult New Zealand Black (NZB) mouse cells were studied. Cultures of NZB embryo (NZB-ME) and other mammalian cells were checked for the presence of MuLV by detection of the group-specific (gs), complement-fixing (CF) antigen. Cultures were also examined for the induction of plaques after cocultivation with XC cells. Virus genome rescue was also attempted by cocultivation of HT-1, NRK-Harvey, or MSV-8 cells; with the tissue being assayed fo for NZB-MuLV. The distribution of NZB-MuLV in NZB mice was determined by focus formation assays, and the ability of the NZB-MuLV present in NZB-ME cells to "help" in focus formation by MSV was also determined. NZB-MuLV was recovered from over 50 adult NZB mice and 15 NZB embryos. Its presence was best detected by measuring its ability to rescue MSV genome from a non-virus-producing MSV-transformed rat cell. The virus was able to serve as a helper for the replication of MSV. In addition, it was found to have a distinct type-specific coat and was a prototype for a third serotype of mouse type C viruses, NZB. The xenotropic virus showed a wide host range, being able to infect even avian cells. It was produced spontaneously by all cells cultivated from NZB tissues and accounted for the high concentration of viral antigens associated with NZB tissues. The extent of virus production was similar in male and female mice, and all cell clones established from embryos also produced it. A variability in the intracellular regulation of virus replication was suggested because tissue cells from the same animal differed quantitatively in their ability to produce xenotropic viruses. The xenotropic virus may have an evolutionary role, and since enhanced spontaneous virus production is associated with cells from NZB mice, the virus may play a role in the autoimmune disease observed in this mouse strain.

4381 MACROMOLECULAR SYNTHESIS IN CELLS INFECTED WITH FROG VIRUS 3. III. VIRUS-SPECIFIC PROTEIN SYNTHESIS BY TEMPERATURE-SENSITIVE MUTANTS. (Eng.) Goorha, R. (St. Jude Children's Res. Hosp., P.O. Box 318, Memphis, Tenn. 38101); Naegele, R. F.; Purifoy, D.; Granoff, A. *Virology* 66(2):428-439; 1975.

Six temperature-sensitive (ts) mutants of frog virus 3 (FV 3), five DNA^{+} and one DNA^{-}, representing six separate complementation groups, were examined for their intracellular patterns of virus-specific protein synthesis at both the permissive (23 C) and nonpermissive (30 C) temperatures. To unmask the viral proteins, protein synthesis in the host fathead minnow (FHM) cells was inhibited by exposing the cells to heat-inactivated Δ mutant. The cells were then exposed to infectious virus and incubated at 23 or 30 C. At 2, 4, and 8 hr after viral infec-

tion, medium containing 25 μCi/ml of reconstituted ^{3}H-labeled protein hydrolysate was added to the cultures. After 30 min, the cells were disrupted and the cytoplasmic extract was analyzed by polyacrylamide-gel electrophoresis, ^{14}C-labeled wild-type FV 3 serving as a standard marker for the virion structural proteins. At the permissive temperature, protein synthesis and its regulation by each mutant was similar to wild type, whereas at the nonpermissive temperature all proteins were detected but some had altered rates of synthesis, indicating defective regulation by 3 of the 6 ts mutants. The six mutants were divided into three categories based on the time and nature of the ts defect during the replication cycle. The first category included three mutants, each representing a separate complementation group, in which virus-specific protein synthesis and its regulation were apparently normal at the nonpermissive temperature. These mutants showed defects in the virus maturation and assembly process suggesting the participation of several FV 3 genes in the assembly process. The second category consisted of a single mutant that had an early defect in the regulation of viral protein synthesis; consequently, a late pattern of virus-specific protein (VSP) synthesis was absent in cells infected with this mutant at the nonpermissive temperature. The third category included the remaining two mutants, both of which were unable to regulate the rate of synthesis of certain VSPs but which had some features of the late pattern of virus-specific protein synthesis. The data confirm and extend the evidence for temporal control over the rate of viral protein synthesis during FV 3 infection. This control appears to be mediated through several viral regulatory proteins.

4382 REGULATION BY THYMIDINE MONOPHOSPHATE AND OTHER NUCLEOTIDES OF THYMIDINE KINASE ACTIVITY IN EXTRACTS FROM PRIMARY RABBIT KIDNEY CELLS INFECTED BY HSV TYPES 1 AND 2. (Eng.) Just, I. (Inst. Medical Microbiology, Univ. Mainz, 65 Mainz, West Germany); Dundaroff, S.; Falke, D.; Wolf, H. U. *J. Gen. Virol.* 29(1):69-80; 1975.

In an attempt to differentiate between thymidine kinase induced by herpesvirus hominis type 1 (TK1) and type 2 (TK2), the different effects of thymidine analogue metabolites on the activities of the two enzymes were studied. Twenty-four hr postinfection, primary rabbit kidney cells and baby hamster kidney 21 cells infected with TK1 and TK2 were homogenized and the supernatant fluids were assayed for thymidine kinase. The influence of pyrimidine nucleosides on thymidine kinase activity was studied in a dose-response fashion and before and after polyacrylamide gel electrophoresis of the enzymes. The enzymatic activity of the crude extracts of the infected cells catalyzed thymidine phosphorylation 10-20 times faster than the phosphorylation of other substrates (e.g., uridine, 2'-deoxyuridine, and 2'-deoxycytidine, but when these substrates were added together with radioactive thymidine, no interference with the phosphorylation of thymidine was seen. 2'-Deoxythymidine-5'-triphosphate (dThd-5'-PPP) inhibited TK2 by 90% at a concentration of 0.125 mM, whereas TK1 was inhibited only 50% at a concentration of 4.03 mM. 2'-Deoxythymidine-5'-monophosphate (dThd-5'-P) competitively inhibited TK2 at all concentrations tested, but its effect on TK1 was concentration-dependent; at 500 μM, it stimulated TK1 activity, while at 8 mM it inhibited it. During enzyme kinetic studies, TK1 displayed substrate inhibition which was reversed by dThd-5'-P, but after polyacrylamide gel electrophoresis, the stimulation by dThd-5'-P disappeared. The results suggest the existence on the TK1 molecule of a second binding site for 2'-deoxythymidine which mediates substrate inhibition and which can also be occupied by dTdh-5'-P; the second binding site appears to be separated from the catalytic center.

4383 MAREK'S DISEASE VIRUS (KEKAVA STRAIN) REPLICATION IN CHICKENS, CHICK EMBRYOS AND CELL CULTURES. (Eng.) Yakovleva, L. S. (Inst. of Experimental and Clinical Oncology, U.S.S.R. Acad. of Medical Sciences, 115478 Moscow, U.S.S.R.); Mazurenko, N. P.; Gunenkova, N. K.; Vinogradov, V. N.; Pavlovskaya, A. I.; Chernyakhovskaya, I. *Acta Virol.* 19(4):293-298; 1975.

The Kekava strain of Marek's disease virus (MDV-Kekara) was passaged *in vivo*, *in ovo*, and *in vitro*. In the course of 12 passages of MDV-Kekava in chickens, the morbidity varied greatly (from 23-50%). MDV-Kekava produced plaques in cultures of chick embryo kidney and adult chicken kidney cells and chick embryo fibroblasts (CEF). The virus adaptation to the cultures was very slow. MDV-Kekava induced the formation of pocks on the chorioallantoic membranes (CAM) of chick embryos, but the proportion of embryos with CAM lesions did not exceed 24%. Serial passaging of the virus in chick embryos beyond the fifth passage was unsuccessful. The results of virus isolation in chickens, cell cultures and chick embryos indicate the possibility of a long-term latent virus carrier state in chickens without development of tumors.

4384 MURINE LEUKEMIA VIRUS: DETECTION OF UNINTEGRATED DOUBLE-STRANDED DNA FORMS OF THE PROVIRUS. *(Eng.)* Gianni, A. M. (Istituto di Patologia Generale I, Facolta di Medicina, Universita Statale di Milano, Italy); Smotkin, D.; Weinberg, R. A. *Proc. Natl. Acad. Sci. U.S.A.* 72(2):447-451, 1975.

Two forms of double-stranded viral DNA were found which proved to be putative intermediates in the flow of viral genetic information between the virion RNA and the integrated viral DNA genome. Roller bottle cultures of mouse bone marrow (JLS V-9) cells were infected with 10^{7} PFU/ml of Moloney murine leukemia virus, and the viral DNA was extracted from the infected cells. Viral DNA was detected in hybridization tests using either [^{3}H]-cDNA or [^{125}I]-RNA, and proviral DNA was assayed by incubation with either of these probes. Both strands of viral DNA appeared to reach a plateau within six hours of infection, although the DNA complementary to [^{125}I]-labeled RNA reached its maximum prior to the DNA complementary to the [^{3}H]-DNA probe. The degree of hybridization of both probes was comparable. Centrifugation of the pro-

viral DNA in CsCl under conditions of isopycnic banding resulted in one band of detectable proviral DNA at a density of 1.7133. Additional fractionation of the proviral DNA on an ethidium bromide CsCl (EtBr-CsCl) gradient showed that a substantial proportion of the DNA banded at a density indicative of a closed double-stranded circular DNA. In a neutral sucrose gradient, the DNA from the dense band in the EtBr-CsCl gradients sedimented at a rate of about 30 S, with a smaller, variable shoulder at 19-20 S. After storage for one month at -20 C, the prominent peak was observed at 19 S. In an alkaline sucrose gradient, half of the viral DNA sedimented with a coefficient of 70 S. The DNA found in the less-dense band of the EtBr-CsCl gradient contained two components: the rapidly sedimenting component behaved like double-stranded linear or nicked-circular DNA of 6 x 10^6 daltons, and the slowly sedimenting material appeared to contain DNA fragments of 5 x 10^5 daltons. It was concluded that the DNA found in the denser band of the EtBr-CsCl gradient consisted of double-stranded, closed-circular DNA molecules containing no alkali-labile linkages and of molecular wt 6 x 10^6 daltons.

4385 DEPENDENCE OF MOLONEY MURINE LEUKEMIA VIRUS PRODUCTION ON CELL GROWTH. (Eng.) Paskind, M. P. (Center for Cancer Res., Massachusetts Inst. Technology, 77 Mass. Ave., Cambridge, Mass. 02139); Weinberg, R. A.; Baltimore, D. *Virology* 67(1):242-248; 1975.

The effects of release from growth arrest (G_0) on the production of Moloney murine leukemia virus (M-MuLV) was studied, using a virus-producing clone derived from cells chronically infected with M-MuLV (JLS V-11). The cultures became stationary at subconfluent density three days after seeding and were released from the stationary phase one day later. DNA synthesis was measured after incubation for 1-hr periods with 0.25 μCi/ml of [^{3}H]thymidine. Reverse transcriptase was also assayed using poly(A) x oligo(dT) or poly(C) x oligo(dG) as template primer, and XC-cell assays were used to determine the effects of cycloheximide (10 μg/ml) and actinomycin D (0.1 μg/ml) on virus release. Finally, a poly(U)-filter assay was used to determine whether the first wave of virus particles released after the resumption of cell growth utilized preexisting viral RNA. The production of M-MuLV ceased in the stationary JLS V-11 cells. Stimulation of the cells to reenter the growth cycle synchronously was followed by two waves of virus release. The first wave, occurring within four hours after the cells were released from G_0, was unaffected by actinomycin D; the second wave, coinciding roughly with the mitotic period of the following cell cycle, was prevented by actinomycin D. Both waves of virus release were inhibited by cycloheximide. Thus, the first wave of released virus appeared to contain viral RNA which was already present in the resting cells, while the second wave of released virus particles carried newly formed viral RNA. The results further suggest that some form of translational, rather than transcriptional, control is responsible for the reinitiation of virus production during the transition from quiescence to growth.

4386 KINETICS OF PROPAGATION OF B-TROPIC MURIN LEUKEMIA VIRUS ON Fv-1^b CELL LINES: REQUIREMENT FOR MULTIPLE CYCLES OF CELL REPLICATION FOR TRANSFORMATION AND VIRAL ANTIGEN EXPRESSION BY RadLV. (Eng.) Decleve, A. (Stanford Univ. Sch. Me Calif.); Niwa, O.; Gelmann, E.; Kaplan, H. S. *Virology* 63(2):367-383; 1975.

The kinetics of intracellular viral antigen production in Fv-1^b cell lines; UCl-B, BALB/3T3, and BL-5 and of focus formation in UCl-B cells were investigated. The cells were previously infected with several 5- to 10-fold dilutions of RadLV*, a naturally occurring B-tropic murine leukemia virus adapted to continuous propagation *in vitro*; the cells were als infected with infective centers of BL-5(RadLV) cell chronically infected with RadLV*. Whereas such infective centers induced focus formation in UCl-B ce with high efficiency within a single culture passag the development of infective center activity in BL- cells infected with free RadLV* both required one o more subcultures and several rounds of cell replica tion. The end point dilution titer was not detecte until 4-5 subcultures and about 15 rounds of cell cycle replication were completed. Viral antigen co tent, measured by indirect immunofluorescence, followed a triphasic pattern with respect to time and viral input concentration. However, both the indirect immunofluorescence assay at three days and the focus formation assay at seven days (one subculture were characterized by single-hit kinetics, excludin the possibility that mutual complementation of defective dLV* particles might account for the delaye expression of viral infection. When viral replication was related to the number of rounds of cell re plication, rather than to elapsed time, no significant differences among the three cell lines were observed. As in previous studies with NB-tropic vi ruses, RadLV* failed to rescue a putative sarcoma virus from UCl-B cells. It is concluded that RadLV is not defective, and can replicate to high titer i several Fv-1^b cell lines in the absence of a detect able murine sarcoma virus genome. However, the kin tics of its replication suggest that certain expres sions of infection may be dependent upon the attain ment of a threshold level of some viral products, t synthesis of which is dependent upon sustained cell proliferation.

4387 NON-PRODUCER HUMAN CELLS INDUCED BY MURINE SARCOMA VIRUS. (Eng.) Rhim, J. S. (Microbiological Associates, Inc., Bethesda, Md. 20014); Cho, H. Y.; Huebner, R. J. *Int. J. Cancer* 15(1):23-29; 1975.

Nonproducer (NP) human cells were isolated from transformed foci induced by the Kirsten mouse sarcoma virus. These morphologically altered NP cells produced neither infectious virus nor complement-fixing antigens of the murine sarcoma-leukemia virus complex. However, the sarcoma virus genome could be rescued from these NP cells by co-cultivation with cells carrying "helper" Kirsten mouse leukemia virus of Woolly Monkey Leukemia virus. The possible usefulness of these cells in efforts designed to detect covert or repressed RNA tumor viruses in various animal and human tissues is discussed. The

NP cells may provide an *in vitro* method for the isolation and identifcation of putative RNA tumor viruses from certain human tumors or human tissues such as placenta. They may also provide opportunities for rapid detection of primate viruses and of murine and feline xenotropic viruses and have implications for chemical and viral carcinogenesis.

4388 IDENTIFICATION OF THE 5' END OF ROUS SARCOMA VIRUS RNA. (Eng.) Keith, J. (Dept. Molecular Biology and Virus Lab., Univ. California, Berkeley, Calif. 94720); Fraenkel-Conrat, H. *Proc. Natl. Acad. Sci. USA* 72(9):3347-3350; 1975.

The 5'-terminal triphosphate of the 35S RNA isolated from Rous sarcoma virus (RSV) was identified. ^{32}P- or ^{3}H-labeled RSV RNA preparations were treated with pancreatic and T2 RNase plus bacterial alkaline phosphatase and snake venom phosphodiesterase; this was followed by terminal periodate oxidation and aniline-catalyzed elimination of the RNA or of the nuclease- and phosphatase-resistant fragments. The solution was then analyzed by paper electrophoresis and paper chromatography. Electrophoresis after nuclease-phosphatase degradating yielded a nuclease- and phosphatase degradation yielded a nuclease- and phos- 0.04% of the total labeled RNA. Electrophoresis of this fragment yielded quantitatively similar radioactive spots located in the area of guanylic acid, cytidylic acid, inorganic phosphate, and 7-methylguanylic acid. Chromatography showed that all the radioactivity electrophoretically corresponding to cytidylic acid was actually pC, whereas that associated with guanylic acid behaved in good part (79%) as expected for 2'-O-methylpG. Another minor degradation product of the nuclease- and phosphatase-resistant fragment was detected in the pU area. The data suggest that the terminal structure of this and all 35S RSV RNA molecules in $7mG^{5'}$ $ppp^{5'}G^{m}pCp$-. This finding supports the view that RSV RNA represents a (+) strand messenger which may be directly translated upon infection.

4389 PURIFICATION OF TRYPTOPHAN TRANSFER RNA FROM CHICK CELLS AND ITS IDENTITY WITH "SPOT 1" RNA OF ROUS SARCOMA VIRUS. (Eng.) Waters, L. C. (Oak Ridge Natl. Lab., Oak Ridge, Tenn. 37830); Yang, W.-K.; Mullin, B. C.; Nichols, J. L. *J. Biol. Chem.* 250(16):6627-6629; 1975.

Tryptophan transfer RNA from chick cells chromatographs differently in the reverse-phase column chromatographic system 5 (RPC-5) depending on whether it is aminoacylated or not. This property was utilized to prepare pure tryptophan tRNA with a specific acceptor activity of 1640 pM/50 μg RNA. The purification procedure involved aminoacylation of chicken liver tRNA with ^{3}H-tryptophan, separation of aminoacylated from unreacted ^{3}H-tryptophan by DEAE-cellulose chromatography, and rechromatography on RPC-5. Oligonucleotide fingerprints of tryptophan tRNA purified in this manner were identical to those reported for "spot 1" RNA isolated from Rous sarcoma virus. The availability of purified tryptophan tRNA should greatly facilitate studies of RNA tumor virus replication.

4390 STRUCTURE OF B77 SARCOMA VIRUS RNA: STABILIZATION OF RNA AFTER PACKAGING. (Eng.) Stoltzfus, C. M. (Vanderbilt Univ. Sch. Medicine, Nashville, Tenn. 37232); Snyder, P. N. *J. Virol.* 16(5):1161-1170; 1975.

The RNA structure and maturation of Bratislava 77 (B77) sarcoma virus was investigated. A cloned stock of virus was isolated from a single focus of transformed chick embryo fibroblast cells. Plates of cells transformed and producing B77 virus were labeled with [5-^{3}H]uridine and [^{32}P]phosphate; the virus was then purified and RNA extracted. Denaturation of 65S RNA into subunits was prevented by increasing the extraction salt concentration from 0.1 to 0.5 mM NaCl. Pronase digestion of immature RNA resulted in little, if any, nicking. However the proportion of 60-70S RNA to 35S RNA was strongly dependent on the extraction temperature; the rate of stabilization at 45 C was increased four-fold over the rate at 37 C. The incubation temperature also affected the RNA dissociation. A change in T_m, from 56 C to 67.5 C, with increasing virus age was also noted. Evidence suggests that the intersubunit linkages in immature B77 60-70S RNA are unstable and spontaneously dissociate when the virus is extracted with phenol at room temperature in the presence of 0.1 M NaCl. It is further suggested that the observed increase in T_m with virus age results from an increase in stability of base-paired regions.

4391 EFFECT OF SERUM CONCENTRATION ON ADENYLATE CYCLASE ACTIVITIES OF UNTRANSFORMED BHK CELLS AND POLYOMA VIRUS-TRANSFORMED DERIVATIVES. (Eng.) Matsumoto, T. (Sapporo Medical College, Minami-1-jo, Nishi-17-chome, Chuo-ku, Sapporo 060, Japan); Uchida, T. *Gann.* 66(4):393-397; 1975.

Adenylate cyclase activities of untransformed hamster BHK 21/13 cells and their polyoma virus-transformed derivatives were compared using cells cultured in low and high serum concentrations. Untransformed cells cultured in a medium containing 10% serum had an enzyme activity 1.5 times higher than that of transformed cells cultured under the same conditions. When the cells were cultured in a medium containing 0.5% serum that stopped proliferation of untransformed cells, the untransformed cells had a two-fold higher adenylate cyclase activity than the transformed cells. The full activity measured in the presence of 10 mM NaF was two-fold higher in the untransformed than in the transformed cells. The low serum concentration increased the enzyme activity of both untransformed cells, but the enzyme activity of transformed cells in the presence of 0.5% serum did not exceed the activity of untransformed cells in 10% serum. Intracellular cyclic AMP levels paralleled the activity of adenylate cyclase, but no correlation was found between cyclic AMP levels and cyclic AMP phosphodiesterase activities.

4392 HOMOLOGY AND RELATIONSHIP BETWEEN THE GENOMES OF PAPOVAVIRUSES, BK VIRUS AND SIMIAN VIRUS 40. (Eng.) Khoury, G. (Natl. Inst. of Allergy and Infectious Diseases, Bethesda, Md.

20014); Howley, P. M.; Garon, C.; Mullarkey, M. F.; Takemoto, K. K.; Martin, M. A. *Proc. Natl. Acad. Sci. USA* 72(7):2563-2567; 1975.

The polynucleotide sequence homology between Papovavirus BK virus (BKV) DNA and the simian virus 40 (SV40) DNAs was studied, and the common regions were localized on the physical map of SV40 DNA. The respective DNAs were digested with restriction enzymes, and DNA-DNA hybridization experiments were carried out using the minus DNA strain of the 11 ^{32}P-labeled *Hin*d SV40 fragments and a 10- to 20-fold molar excess of ^{3}H-labeled sheared BKV or polyoma DNA. DNA-DNA filter hybridization experiments and DNA-complementary RNA annealing reactions were also performed. *Eco*RI-cleaved linear BKV and SV40 DNAs were denatured and studied by electron microscopy, or the DNAs were added to adenovirus 2+ ND_2 DNA prior to denaturing. The DNA-DNA hybridization studies and analysis of the heteroduplex molecules between *Eco*RI linear molecules of SV40 and BKV DNAs established the portions of the SV40 genome that are homologous to BKV. The shared sequences were located principally in the late gene region of the SV40 DNA, corresponding to portions of *Hin*d fragments C, D, G, J, and K, and to a lesser extent *Hin*d fragments E and F. Little or no homology was detected between BKV DNA and the early region of the SV40 genome. The general location of homologous regions at the termini of the RI-linear molecules and the constant central region of heterology suggested that the BKV and SV40 genomes have the same basic genome. The studies with SV40 complementary RNA further indicated that the strand orientation of the shared nucleotide sequences are the same for both SV40 and BKV. The precise evolutionary relationship of these two agents, is, however, unknown.

4393 THE ALTERATION OF RIBOSOMES FOR mRNA SELECTION CONCERNED WITH ADENOVIRUS GROWTH IN SV40-INFECTED SIMIAN CELLS. (Eng.) Nakajima, K. (Inst. Medical Science, P.O. Takanawa, Tokyo, Japan); Oda, K. *Virology* 67(1)85-93; 1975.

The simian virus 40 (SV40) helper function to support human adenovirus (Ad) growth in African green monkey kidney (AGMK) cells previously infected with SV40 was studied. Confluent monolayer cultures were infected with SV40 (0.2-20 plaque-forming units (PFU)/cell), and 24 hr later were infected with Ad2 (10 PFU/cell). The amounts of DNA and messenger RNA (mRNA) synthesis in these cells were estimated by hybridization of pulse-labeled DNA or RNA with an excess of SV40 or cellular DNA. The amount of Ad2 virion antigens synthesized in the doubly infected cells was estimated by a microcomplement-fixation test. Protein synthesis with preincubation S30 (prepared from SV40-infected cells) was studied to determine the alteration of the protein synthesizing system to be able to translate late Ad2 mRNA for hexon. Formation of the 80S initiation complex for protein synthesis was carried out in the presence of high salt-washed ribosomes from preincubation AGMK cell S30, Met-transferRNA, and ^{3}H-labeled late Ad2 mRNA (24S). The effect of input multiplicities on the alteration of ribosomes was also investigated. The SV40 helper function to support human adenovirus growth in SV40-infected AGMK cells was apparently mediated by an alteration of ribosomes to translate late Ad2 mRNA. The amount of Ad2 capsid proteins synthesized was proportional to that of SV40 mRNA and SV40-induced cellular mRNA synthesized before synthesis was suppressed by Ad2 infection. These amounts were increased in parallel with the increase in the fraction of SV40 T antigen-positive cells in culture. An alteration in the preincubated S30 from the SV40-infected cells to respond to late Ad2 mRNA (24S) to synthesized hexon occurred nearly 15 hr after infection. This alteration was caused by the appearance of a new initiation factor for protein synthesis which modifies ribosomes and occurred irrespective of the induction of cellular DNA synthesis. A close correlation was observed between the amount of Ad2 capsid proteins synthesized in the doubly infected cells and the proportion of ribosomes altered to respond to late Ad2 mRNA. These results indicate that a certain early SV40 gene product acts to induce a new initiation factor for protein synthesis.

4394 STUDIES ON THE REGULATION OF DEOXYPYRIMIDINE KINASES IN NORMAL SV40-TRANSFORMED AN SV40- AND ADENOVIRUS-INFECTED MOUSE CELLS IN CULTURE (Eng.) Postel, E. H. (Dept. Biochem. Sci., Princeto Univ., N.J.); Levine, A. J. *Virology* 63(2):404-420; 1975.

The regulation of cellular deoxypyrimidine kinases i normal, transformed, and abortively infected mouse cells was investigated under a variety of physiological conditions to determine how viral gene products alter the expression of normal cellular functions. Deoxythymidine kinase, deoxyuridine kinase, and deox cytodine kinase were each found to be present in mul tiple enzymatic forms in mouse cells. Actively grow ing 3T3 cells in culture expressed a substrate-speci fic deoxycytidinase kinase and a deoxythymidine diox uridine kinase activity. Resting cells in culture contained two electrophoretically distinct deoxypyrimidine kinase activities that phosphorylated all three deoxypyrimidine nucleoside substrates. The sa kinases detected in actively growing cells in cultur were the major enzymatic activities observed in feta or young mice, while adult mice expressed predominantly those activities found in resting cells in ti sue culture. Thus, the expression of the mouse deox pyrimidine kinase reflects alterations in cell growt indicating that their regulation was governed by the physiological state of the cells. Simian virus 40 (SV40)-transformed derivatives of three different mouse cell lines (Swiss-3T3, BALB C-3T3 and 129-3T3) displayed a qualitatively normal mode of deoxypyrimidine kinase regulation. Growing transformed cells expressed the growing form of these enzymes, while resting transformed cells at very high saturation densities contained the normal resting cell kinases. When normal resting 3T3 cells were abortively infecte with SV40 or adenovirus, there was a large increase i the specific activity of only the growing cell specific kinases. The results show that the deoxypyrimidine kinases are apparently regulated by the physiological state of the cells.

4395 STIMULATION OF ADENOVIRUS REPLICATION IN SIMIAN CELLS IN THE ABSENCE OF A HELPER VIRUS BY PRETREATMENT OF THE CELLS WITH IODODEOXYURIDINE. (Eng.) Jerkofsky, M. (Milton S. Hershey Med. Cent., Pennsylvania State Univ., Hershey); Rapp, F. *J. Virol.* 15(2):253-258; 1975.

The effect of 5'-iododeoxyuridine (IUdR)-pretreatment on the susceptibility of primary African green monkey kidney (GMK) cells to infection by human adenovirus 7 was investigated. Primary GMK cells were trypsinized and sedimented, and then resuspended in media containing various concentrations of IUdR or in drug-free media. At confluency, the drug was removed; virus (3-5 plaque forming units/cell) was then added and allowed to adsorb for 1-2 hr at 37 C. Cells were pulsed for two hours at 22 hr postinoculation with 10 µCi tritiated thymidine/ml. Density gradient centrifugation analysis was performed with some samples. At all concentrations of IUdR (0, 10, 50 and 100 µg/ml), there was a decrease in the efficiency of Simian virus 40 (SV40) replication. This was true even at 50 µg/ml, at which the replication of adenovirus 7 was maximally enhanced; this decrease did not affect its ability to enhance the replication of adenovirus 7. The number of infectious centers remained unchanged after IUdR pretreatment, but the burst size of virus from each infected cell increased. Cell DNA synthesis was stimulated in pretreated cells infected with adenovirus 7, but the host cell DNA synthesized was small enough to remain in the Hirt supernatant fluid. The modification of susceptibility to adenovirus replication and the changed pattern of cell DNA synthesis was stable for at least two additional cell passages of the pretreated cells. Pretreatment with IUdR does not change the number of cells capable of producing infectious adenovirus, but the amount of adenovirus produced by each infected cell is increased. Therefore, it appears that IUdR pretreatment allows each infected cell to produce virus more efficiently.

4396 SIMIAN VIRUS 40-SPECIFIC PROTEINS IN HeLa CELLS INFECTED WITH NONDEFECTIVE ADENOVIRUS 2-SIMIAN VIRUS 40 HYBRID VIRUSES. (Eng.) Walter, G. (Tumor Virology Lab., Salk Inst., Post Office Box 1809, San Diego, Calif. 92112); Martin, H. *J. Virol.* 16(5):1236-1247; 1975.

The synthesis of simian virus 40 (SV40)-specific proteins in HeLa cells infected with the nondefective adenovirus 2 (Ad2)-SV40 hybrid viruses, $Ad2^+$ ND2, $Ad2^+$ ND3, $Ad2^+$ ND4, and $Ad2^+$ ND5, was investigated. Infected-cell proteins were first detected 23 hr after infection; their synthesis continued late in infection when host protein synthesis was shut off. All polypeptides normally seen in Ad2-infected cells were found in cells infected by the hybrid viruses. In addition to the Ad2-specific proteins, cells infected with $Ad2^+$ ND2 contain two SV40-specific proteins with apparent molecular weights of 42,000 and 56,000, cells infected with $Ad2^+$ ND4 contain one protein with an apparent molecular wt of 56,000, and cells infected with $Ad2^+$ ND5 contain one protein with an apparent molecular wt of 42,000. Cells infected with $Ad2^+$ ND3 do not contain detectable amounts of proteins not seen during Ad2 infection. Pulse-chase experiments demonstrate that the SV40-specific proteins induced by $Ad2^+$ ND2, $Ad2^+$ ND4, and $Ad2^+$ ND5 are metabolically unstable, disappearing almost completely in 12 hr. These proteins are not present in purified virions. Two nonstructural Ad2-specific proteins have been demonstrated in Ad2 and hybrid virus-infected cells which have a smaller apparent molecular wt after a short pulse than after a pulse followed by a chase. The molecular wt increase during the chase may be cuased by the addition of carbyhydrate to a polypeptide backbone.

4397 ELECTRON MICROSCOPE LOCALIZATION OF A PROTEIN BOUND NEAR THE ORIGIN OF SIMIAN VIRUS 40 DNA REPLICATION. (Eng.) Griffith, J. (Stanford Univ. Med. Cent., Calif.); Dieckmann, M.; Berg, P. *J. Virol.* 15(1):167-172; 1975.

Electron microscopy was utilized in investigating the location and possible function of a stably bound protein "knob" on simian virus 40 (SV40) DNA. Monkey kidney cell cultures (CU-1) infected with SV40 virus (strain Rh9 11) were used. Throughout infection of the cultures by SV40 virus, most of the viral DNA existed as a non-encapsulated, nucleoprotein complex. After Triton X-100 extraction and incubation with 1 M NaCl, however, a new, high salt-stable protein-DNA complex was discovered. Examination by high resolution electron microscopy, revealed the tightly twisted rods characteristic of SV40 form 1 DNA. Nicking by brief X-ray treatment yielded circular structures containing one "knob" per DNA molecule as the predominant molecular species. Disruption of purified virus particles and CsCl gradient banding revealed structures closely resembling the salt-stable protein-DNA complexes recovered directly from the infected cells. Cleavage of the salt-stable protein-DNA with *eco* R1 endonuclease yielded unit length linear molecules, with the "knobs" occurring predominantly at 0.64-0.75 SV40 fractional lengths from the farther end. Cleavage with *hpa*II endonuclease set the location of the "knobs" at 0.70 ± 0.05 on the SV40 DNA map. Thus, high resolution electron microscopy has located the site of the 2 or 3 globular protein unit "knob". Speculations on the function and genetic origin of the stably bound protein on the SV40 DNA as related to location suggest a role in initiating DNA replication or promoting some essential step in expression.

4398 ^1H AND ^{13}C NUCLEAR MAGNETIC RESONANCE SPECTRA OF THE LIPIDS IN NORMAL AND SV 40 VIRUS-TRANSFORMED HAMSTER EMBRYO FIBROBLAST MEMBRANES. (Eng.) Nicolau, C. (Institut fur Strahlenchemie im Max-Planck-Institut fur Kohlenforschung, 433 Mulheim a. d. Ruhr West Germany); Dietrich, W.; Steiner, M. R.; Steiner, S.; Melnick, J. L. *Biochim. Biophys. Acta* 382(3):311-321; 1975.

Well-resolved ^1H and ^{13}C nuclear magnetic resonance spectra were obtained with normal and simian virus 40-transformed membranes of hamster embryo fibroblasts. Estimation of the ratio of $^{13}CT_2$ values of the normal to transformed cell membranes showed an increased intermolecular motion in the transformed cell membranes. The temperature dependence of the

$(CH_2)n$ line in the ^1H spectra in the range 298-343 K showed an activation energy for the lateral diffusion of the fluid phospholipid regions in the normal cell membranes while the transformed ones showed practically no temperature dependence in this temperature range. The fluidity of the phospholipid region in the transformed cell membrane seems to be significantly higher than that observed in the normal cell material. These data support and extend the findings concerning the mobility of the concanavalin A binding/agglutinizing sites on the surface of normal and virus-transformed cells and suggest further approaches to the study of the membrane alterations in tumor cells.

4399 DNA INFECTIVITY AND THE INDUCTION OF HOST DNA SYNTHESIS WITH TEMPERATURE-SENSITIVE MUTANTS OF SIMIAN VIRUS 40. (Eng.) Chou, J. Y. (Natl. Inst. Arthritis Metab. Dig. Dis., Bethesda, Md.); Martin, R. G. *J. Virol.* 15(1):145-150; 1975.

The induction of host DNA synthesis and the initiation of viral DNA synthesis (infectivity) were studied in mutant classes of Simian virus 40 (SV40). DNA extracts were prepared from SV40-infected CV-1 cell monolayers at a concentration of five plaque-forming units (PFU)/cell. Infectivity was studied *via* experiments: equal parts of a DNA solution prepared from the extracts and virus suspension containing 2 x 10^6 PFU/ml were added to confluent monolayers of CV-1 cells. For induction experiments, cells were labeled by incubation for one hour with 1.5 ml of modified Eagle medium without serum supplement containing 100 µCi/ml ^3H-thymidine. DNA from D-mutant class was infective at 40 C (D101 yielded 2 x 10^5 PFU/ml), while A, B, C, and BC were significantly less infective (A207, 20 PFU/ml; B201, 2.4 x 10^2 PFU/ml; C260, 3 x 10^2 PFU/ml; BC230, 2 PFU/ml). Coinfection of A virions with wild-type or D-mutant DNA did not enhance viral replication (A209 virion + D202 DNA, 17.1 counts/min thymidine uptake; A209 + wild type DNA, 31.5 counts/min; D202 DNA, 20.9 counts/min; wild type DNA, 29.1 counts/min). A-mutants were defective in inducing host DNA synthesis at 42.5 C (A241, 42.5 C, 14.8 x 10^3 counts/min; 33 C, 25.2 x 10^3 counts/min). It is suggested that the D function is not required for the production of infectious virions. It is also concluded that the A function is pleiotropic, being required for both the initiation of viral DNA synthesis and the induction of host DNA synthesis.

4400 DETECTION OF AN ANTIGEN RELATED TO MASON-PFIZER VIRUS IN MALIGNANT HUMAN BREAST TUMORS. (Eng.) Yeh, J. (John L. Smith Memorial Inst. for Cancer Res., Pfizer Inc., Maywood, N. J. 07607); Ahmed, M.; Mayyasi, S. A.; Alessi, A. A. *Science* 190(4214):583-584; 1975.

A protein antigenically related to the Mason-Pfizer monkey virus (M-PMV) p27 was detected in human malignant breast tumors. Frozen malignant breast tumors selected after gross and microscopic pathological examination were homogenized and extracted with ether. The soluble proteins were futher purified by diethylaminoethyl-cellulose ion exchange column chromatography, and the fractions expected to elude p27 collected and concentrated. Of 18 breast tumor specimens tested, eight induced the release of 25% of the maximum precipitable ^{125}I-labeled M-PMV p27; the range of ^{125}I release was 27-78%. Each of the tumor specimens showed competition curves of similar slope to that developed with purified M-PMV as the competing antigen, suggesting similar reacting proteins. The amount of p27-like proteins detected ranged from 0.3 to 5.7 ng/mg of tissue extract. No detectable antigen related to M-PMV was found in 12 human tumors of other origin, or two normal placentas tested. Furthermore, nonspecific competition by the malignant breast tissue extracts was eliminated *via* their lack of competition against SSV-1 p30. Partially purified tissue material quantitatively tested for p27 by competition radioimmunoassay revealed a 50% recovery of the p27 after purification procedures, and suggested a very low level of viruslike antigens in malignant breast tissue.

4401 INDUCTION OF ENDOGENOUS AND OF SPLEEN FOCUS FORMING VIRUSES DURING DIMETHYLSULFOXIDE-INDUCED DIFFERENTIATION OF MOUSE ERYTHROLEUKEMIA CELLS TRANSFORMED BY SPLEEN FOCUS-FORMING VIRUS. (Eng.) Dube, S. K. (Max-Planck Institut fur Experimentelle Medizin, Gottingen, West Germany); Pragnell, I. B.; Kluge, N.; Gaedicke, G.; Steinheider, G.; Ostertag, W. *Proc. Natl. Acad. Sci. USA* 72(5):1863-1867; 1975.

Mouse erythroleukemia cells in culture provided an opportunity to study the role of the erythroid cell-transforming spleen focus-forming virus (SFFV) during dimethylsulfoxide (Me_2SO)-induced erythroid differentiation of these cells. Me_2SO (1 or 1.5%) induced erythroid differentiation and a 10- to 100-fold increase in spleen focus formation in an erythroleukemic cell clone established by infection of N type DBA/2 mice with NB tropic SFFV. This induction was correlated with the induction of globin messenger RNA synthesis. No increase in virus induction occurred in a clone of SFFV-transformed cells that do not differentiate in the presence of Me_2SO, indicating that induction of virus release is dependent on erythroid differentiation. The Friend virus (FV) complex released by uninduced cells was NB tropic, since it resulted in a comparable increase in spleen focus formation in N type DBA/2 and B type BALB/c mice. The virus released by Me_2SO-induced cells was N tropic, as it induced a 20-fold increase in spleen focus formation in DBA/2 mice but no detectable increase in BALB/c mice. To determine if the induced virus was exclusively N tropic endogenous virus, the effects of externally added NB tropic LLV-F helper virus, the second component of the FV complex, were studied. Added NB tropic LLV-F did not increase the number of spleen focus-forming units released by either uninduced or induced cells, but did induce identical increases in SFFV titers in B and N type mice. Me_2SO therefore induces SFFV as well as an endogenous virus. This joint induction could mean that transformed cells release a nondefective endogenous virus with the ability to transform erythroid cells. The data indicate that the endogenous virus and the erythroid focus-forming virus interact during Me_2SO-induce erythroid differentiation.

4402 VACCINIA VIRUS INFECTION OF HeLa CELLS. I. SYNTHESIS OF VACCINIA DNA IN HOST CELL NUCLEI. (Eng.) LaColla, P. (Roche Inst. Mol. Biol., Nutley, N.J.); Weissbach, A. *J. Virol.* 15(2):305-315; 1975.

The synthesis of vaccinia DNA in host cell nuclei was investigated using DNA-DNA hybridization techniques. Membrane filters containing vaccinia DNA (5 μg/filter) extracted from nuclei of uninfected cells, were made using Sartorius nitrocellulose membranes. The input ^{3}H DNA was denatured by incubating in 0.3 N NaOH at 37 C for 15 min. Hybridizations were carried out at 65 C for 36 hr. The [^{3}H]thymidine pulse-labeled vaccinia DNA synthesized in the nucleus of HeLa S3 cells reached a maximum at about three hours after infection, corresponding to the time of maximal DNA synthesis in infected cells. At this time host DNA synthesis dropped to about 25% of the rate of the uninfected cells. Even with short labeling times (two minutes), the nucleus contained 60% of the incorporated [^{3}H]thymidine, much of which was in vaccinia DNA. Prior inhibition of host nuclear DNA synthesis with mitomycin C, followed by removal of the antibiotic, caused a subsequent inhibition of vaccinia DNA synthesis and complete suppression of mature virus. Purified nuclei, isolated from vaccinia-infected cells, also synthesized vaccinia DNA *in vitro*. Over 90% of the DNA synthesized *in vitro* by isolated nuclei contained vaccinia-specific sequences. The results suggest that both the nucleus and cytoplasm are involved in the replication of vaccinia virus, and that host DNA synthesis is only partially suppressed during viral development.

4403 ANTILYMPHOCYTE-ANTIVIRAL ACTIVITIES OF A FACTOR(S) PRODUCED BY A HERPESVIRUS SAIMIRI (HVS) MARMOSET TUMOR DERIVED CELL LINE (MLC-1) [abstract]. (Eng.) Neubauer, R. H. (Litton Bionetics, Inc., Kensington, Md.); Wallen, W. C.; Rabin, H. *Proc. Am. Assoc. Cancer Res.* 16:13; 1975.

4404 STUDIES OF MAREK'S DISEASE HERPESVIRUS AND TURKEY HERPESVIRUS SPECIFIC COMMON ANTIGEN WHICH STIMULATES THE PRODUCTION OF NEUTRALIZING ANTIBODIES. (Eng.) Onuma, M. (Faculty Veterinary Medicine, Hokkaido Univ., Sapporo, Japan); Mikami, T.; Hayashi, T. T. A.; Okada, K.; Fujimoto*, Y. *Arch. Virol.* 48(1):85-97; 1975.

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4406 INHIBITION BY PHOSPHONOACETIC ACID OF CELLS TRANSFORMED WITH INACTIVATED HERPES SIMPLEX VIRUS [abstract]. (Eng.) Duff, R. (Abbott Lab., North Chicago, Ill.). *Proc. Am. Assoc. Cancer Res.* 16:39; 1975.

4407 EFFECTS OF 5-TUNGSTO-2-ANTIMONIATE (HPA-23) IN ONCOGENIC DNA AND RNA VIRUS-CELL SYSTEMS [abstract]. (Eng.) Ablashi, D. V. (Natl. Cancer Inst., Bethesda, Md.); Twardzik, D. R.; Easton, J. M.; Armstrong, G. R.; Luetzeler, J.; Jasmin, C.; Chermann, J. C. *Proc. Am. Assoc. Cancer Res.* 16:31; 1975.

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4409 TRANSFORMATION OF CULTURED RAT ADRENOCORTICAL CELLS BY KIRSTEN MURINE SARCOMA VIRUS [abstract]. (Eng.) Auersperg, N. (Cancer Res. Centre, Univ. British Columbia, Vancouver, B.C. V6T 1W5, Canada); Jull, J. W.; Hudson, J. B.; Goddard, E. J. *Proc. Am. Assoc. Cancer Res.* 16:67; 1975.

4410 DIFFERENCES IN DETECTION OF SIMIAN SARCOMA VIRUS 70S RNA AND REVERSE TRANSCRIPTASE IN CELLS CULTURED *IN VITRO* AND *IN VIVO* [abstract]. Saxton, R. E. (Div. Surg. Oncol., Univ. California Los Angeles); Rangel, D.; Morton, D. L. *Proc. Am. Assoc. Cancer Res.* 16:171; 1975.

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4413 COMPARATIVE ANALYSIS OF PLASMA MEMBRANES OF NORMAL AND TRANSFORMED CELL PHENOTYPES [abstract]. (Eng.) Nigam, V. N. (Cell Biology, University of Sherbrooke, Quebec, Canada); Brailovsky, C. *Proc. Am. Assoc. Cancer Res.* 16:196; 1975.

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4419 TUMORIGENICITY IN *NUDE* MICE OF VIRUS TRANSFORMED CELLS IS CORRELATED SPECIFICALLY WITH ANCHORAGE-INDEPENDENT GROWTH *IN VITRO* [abstract]. (Eng.) Freedman, V. H. (Albert Einstein Coll. Medicine, Bronx, N.Y.); Shin, S. *Genetics* 80(3/Part 1/Suppl.):s32; 1975.

4420 EPSTEIN-BARR VIRUS IN INFECTIOUS MONONUCLEOSIS AND BURKITT LYMPHOMA [abstract]. (Eng.) Gerber, P. (Food and Drug Adm., Bethesda, Md.); Nkrumah, F. K.; Prichett, R.; Kieff, E. *Proc. Am. Assoc. Cancer Res.* 16:23; 1975.

4421 CHARACTERISTICS OF CELLULAR TRANSFORMATION ASSOCIATED WITH THE EPSTEIN-BARR VIRUS IN NON-LYMPHOBLASTOID CELLS [abstract]. (Eng.) Glaser, R. (M. S. Hershey Med. Cent. Pennsylvania State Univ., Hershey, Pa.); Decker, B.; Ladda, R.; Shows, T. B. *Proc. Am. Assoc. Cancer Res.* 16:70; 1975.

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4426 EFFECT OF DEXAMETHASONE ON THE MOUSE MAMMARY TUMOR VIRUS GROWN IN CAT KIDNEY CELLS [abstract]. (Eng.) Lasfargues, E. Y. (Inst. Med. Res., Camden, N.J.); Dion, A.; Lasfargues, J. C.; Moore, D. H. *Proc. Am. Assoc. Cancer Res.* 16:28; 1975.

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4431 STRAND ORIGIN OF POLYOMA VIRUS-SPECIFIC 'GIANT' NUCLEAR RNA AND 16S AND 19S MESSENGER RNA [abstract]. (Eng.) Acheson, N. H. (ISREC, CH-1011 Lausanne, Switzerland); Beard, P. *Experientia* 31(6):733; 1975.

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See also:

* (Rev): 4212, 4213, 4214, 4215, 4219, 4237, 4238, 4239, 4240, 4241, 4242, 4243, 4244, 4245, 4257, 4263
* (Immun): 4440, 4478, 4480, 4506, 4519, 4529, 4536
* (Path): 4556, 4595
* (Epid-Biom): 4659, 4669

4435 A STUDY OF IMMUNOLOGICAL SPECIFICITY OF TRANSPLACENTALLY INDUCED NEURINOMAS IN RATS. (Rus.) Okulov, V. B. (N. N. Petrov Inst. Oncol., Min. Publ. Health U.S.S.R., Leningrad, U.S.S.R.); Kolodin, V. I. *Vestn. Akad. Med. Nauk SSSR* (2):60-63; 1975.

Tumors of the peripheral nervous system (neurinomas), induced transplacentally in rats with N-nitroso-N-ethyl urea were studied by precipitation in agar and immunoelectrophoresis for their immunological specificity. Females were administered a 40 mg/kg-dose of N-nitroso-N-ethyl urea ip between the 17th and 19th days of gestation. Neurinomas of the peripheral nervous system were found in 17 of 23 animals in the offspring, but no tumor was detected in six animals macroscopically. The tumor was localized in the supramaxillary branch of the trigeminal nerve in 11 cases, in the lumbosacral plexus in three cases, in the nerves of the extremities in two cases, and in the mesenteric plexus of the small intestine in one case. A protein type antigen with the mobility of beta-globulins was detected both in the primary tumor tissue and in transplanted tumors over up to 50 passages. No such antigen was found in extracts of the brain and peripheral nerve tissues in control animals. In 12 out of 14 animals with transplacentally induced primary neurinomas, and in all animals with tumor transplants, the antigen was present in the blood serum. In rats with tumors of other tissues, including tumors induced by nitroso compounds, no neurinoma antigen was found in the tumor or in the serum. The neurinoma antigen was found to differ from other specific proteins in the nerve tissue.

4436 REDUCED CAPACITY TO PRODUCE SPECIFIC 'EFFECTOR' CELLS AFTER INJECTION OF CBA MICE WITH C3H CELLS. (Eng.) Lilliehook, B. (Dept. Tumor Biology, Karolinska Institutet, S-104 01 Stockholm, Sweden); Jacobsson, H.; Blomgren, H. *Scand. J. Immunol.* 4(5/6):463-469; 1975.

A study was made to characterize further the previously demonstrated immunological reactivity of CBA mice to infusion with H-2 compatible, M-antigen-incompatible C3H cells, whereby thymus or peripheral lymphocytes of the infused CBA mice exhibit a decrease in mixed lymphocyte culture (MLC) reactivity with C3H lymphocytes. In the present tests, 1- to 2-month-old CBA mice were injected iv with 10^7 spleen cells from syngeneic mice or from C3H x CBA hybrids. Three weeks later, host-*versus*-graft (HVG) tests were carried out by injecting the host animals with C3H spleen cells into the left footpad and C3H x CBA spleen cells into the right footpad. Enlargement of the local lymph node of the right footpad relative to that of the left occurred in the mice preinjected with syngeneic cells, whereas there was no detectable response in the animals preinjected with C3H x CBA cells. The specificity of C3H x CBA cells for reducing the responsiveness was confirmed by results of further control tests in which CBA x C57Bl cells were used instead of C3H x CBA cells for injection into the right footpad. Lymphocytes from CBA mice showing a decreased HVG response to C3H x CBA spleen cells also showed a reduced capacity to proliferate in spleens of irradiated C3H x CBA mice. These results, like previous results with the MLC test, reflected the efficiency of lymphocytes with respect to being triggered to cell division by foreign transplantation antigens. Although the proliferative capacity of the affected lymphocytes was reduced, their response to C3H x CBA bone marrow target cells was specifically increased. This was revealed by graft-*versus*-host (GVH) tests in which lymph node cells from such mice were injected iv, together with syngeneic bone marrow cells, into irradiated C3H x CBA mice, followed six days later by injection iv of ^{59}Fe citrate; the response of the spleen cells to the target marrow cells was evaluated 16 hr later on the basis of measurements of radioactivity of the spleens of the host animals. These results implied that the infusion of CBA mice with C3H x CBA mice led to the development of certain "effector" cells. In further tests, lymphocytes from normal CBA mice showed a high proliferative rate in spleens of irradiated C3H x CBA mice. Such "educated" cells showed strongly increased specific GVH reactivity. Lymphocytes from CBA mice previously injected with C3H x CBA cells showed, however, a reduced capacity to proliferate when injected into irradiated C3H x CBA hybrids and a poor capacity to develop new "effector" cells reactive against C3H x CBA bone marrow target cells. It appears that lymphocyte proliferation is necessary for the development of specific "effector" cells. Whether the proliferating lymphocytes transform into "effector" cells or recruit other cells into this function remains unknown.

4437 NITROSOMETHYLUREA-INDUCED LYMPHOMAS IN THYMECTOMIZED MICE, IN RELATION TO THYMUS DEPENDENT AND INDEPENDENT SYSTEMS. (Eng.) Palestro, G. (Instituto di Anatomia Patologica I, Universita di Torino, Via Santena 7, I-10126 Torino, Italy); Stramignoni, A. *Oncology* 31(2):115-122; 1975.

Lymphomagenesis was studied in Swiss mice receiving nitrosomethylurea (NMU) at birth and thymectomized 12 days later. In the group given 50 μg NMU, sc, 24 hr after birth, 19 out of 30 mice died before 30 wk of age and none was alive at 60 wk. Thymic lymphomas were found in 18 mice (mediastinal mass, 140-900 mg). The thymic structure was completely distorted. A diffuse proliferation of lymphoid cells was found. Extrathymic organs were involved in 14 animals, most of which died late in the study. All lymphoma-bearing mice died between 19 and 40 wk of age. Among the 12 mice which were tumor-free the thymus weighed between 30-70 mg; histologically the thymic structure was preserved. Pulmonary adenomas were found in 4 out of 18 animals with lymphomas and in 2 out of 12 mice without lymphomas. In the NMU-treated and completely thymectomized group, no thymic or extrathymic lymphomas were found; all mice but one were alive. In this group, 9 of 18 mice developed lung adenomas. In the NMU-treated and incompletely thymectomized group, four mediastinal lymphomas were seen among nine mice. Three also had lung adenomas. All but 3 of 46 intact, untreated mice were alive at 60 wk of age. None of them de-

veloped lymphomas, the only other tumors were two lung adenomas. In these experiments, NMU produced lymphomas only in the thymus and not in extrathymic lymphocytes.

4438 IMPAIRED GROWTH OF A RADIATION-INDUCED LYMPHOMA IN INTACT OR LETHALLY IRRADIATED ATHYMIC (NUDE) MICE. (Eng.) Bonmassar, E. (Natl. Cancer Inst., Building 37, Bethesda, Md. 20014); Campanile, F.; Houchens*, D.; Crino, L.; Goldin, A. *Transplantation* 20(4):343-346; 1975.

Since the allograft reactions of recipient mice against hemopoietic histocompatibility (Hh)-incompatible cells are T-independent, and since reports are lacking for transplantation of allogeneic bone marrow or leukemia cells in nude mice, experiments were carried out to determine whether nude mice would be capable of inhibiting the growth of incompatible lymphoma cells which express Hh alloantigens. Splenic radiation-induced lymphoma L5MF-22 of B10.129(5M) (H-2^b) origin, solid subcutaneous glioma-26 (GL-26) and B16 melanoma (B16M) of C57BL/6 (H-2^b) origin, ascitic L1210 leukemia of DBA/2 (H-2^d) origin, and ascitic Moloney leukemia virus-induced lymphoma LSTRA of BALB/c (H-2^d) origin were used. Nude mice (H-2^d) and various conventional strains of mice (H-2^b or H-2^d) were challenged with tumors of H-2^b or H-2^d genotype and resistance was measured on the basis of number of days until death. It was found that nude mice challenged with H-2-compatible L1210 lymphoma or H-2-incompatible GL-26 or B16 did not show resistance, those challenged with H-2-compatible LSTRA lymphoma showed limited resistance, and those challenged with H-2-incompatible L5MF-22 showed an increase in life span of 142% over conventional syngeneic B10.129(5M) mice. The possibility that the reduced growth of the allogeneic, Hh-incompatible L5MF-22 tumor in nude mice was the result of a conventional allograft reaction appeared to be excluded by results of additional tests which demonstrated a lack of effect of an immunodepressive factor of viral origin (known to inhibit the antilymphoma allograft reaction of conventional mice without affecting anti-Hh allograft responses) and failure of lethal radiation to abrogate the resistance. The data support, therefore, the hypothesis that impaired growth of H-2^b L5MF-22 lymphoma in H-2^d nude mice was the result of a highly efficient anti-Hh allograft reaction. The lack of resistance when mice were challenged with GL-26 or B16 cells is in agreement with the previous observation that Hh antigens are restricted to hemopoietic or lymphoma tissues. The moderate resistance detected with the H-2-compatible LSTRA tumor would be consistent with the previous finding that weak antigens of Hh type can be induced after cell transformation by tumor viruses. The current observations suggested that it might be difficult, without appropriate control of the anti-Hh allograft response, to successfully grow Hh-incompatible leukemias in nude mice.

4439 INFLUENCE OF SUBLETHAL IRRADIATION ON IMMUNE RESPONSE IN MICE TO SHEEP ERYTHROCYTES. (Fre.) Beaumariage, M. L. (Laboratoire d'Anatomie pathologique, Universite de Liege, 1 rue des Bonnes Villes, B 4000 Liege, Belgium); Hiesche, K.; Möller, E.; Revesz, L.; Haot, J. *C. R. Soc. Biol. (Paris)* 169(3):717-723; 1975.

Three hundred and seventy-three male CBA mice, aged two months, were exposed to a 400 R dose of x-rays and injected with SRBC to determine the influence of sublethal irradiation on the immunological response of the spleen to the foreign blood cells. In 185 cases, one of the posterior limbs was shielded from irradiation. Nonirradiated controls numbered 87. The SRBC were injected (2/10 ml of a solution containing 10% RBC) into a lateral vein of the tail of 69 controls and of the irradiated mice, on days 8, 12, 16, 20, and 30 following irradiation. In the hematopoietic marrow of the normal mice, the number of natural rosettes doubled following injection, and remained above the normal value until the end of observations (18 days). After irradiation, the rosette formation capacity (RFC) decreased, and antigenic stimulation had very little effect. After immunization, the RFC rose rapidly in normal mice, with a maximum on day 5 (16 times its normal value). In the irradiated mice, the immunocyte adherence of the splenic cells was significantly reduced and immunological response was more spread out (maximum on days 8 and 12). Response improved if the interval between irradiation and immunization was increased. However, recovery was still incomplete by day 30. The difference between mice irradiated *in toto* and those whose limbs were shielded was insignificant. In nonirradiated mice, cells which secrete immunoglobulin M (IgM) and immunoglobulin G (IgG) (hemolysin-secreting cells:HSC) increased significantly following immunization. Irradiation decreased both types of hemolytic secretions. Results indicate that type B HSCs seem to recover faster than RFCs of B and T origin. The small rise of RFCs in the marrow of nonirradiated mice after immunization is explained by an incapacity of the bone marrow cells to become immunocompetent in the absence of a differentiation process which takes place in a peripheral structure. Bone marrow cells, irradiated or not, respond very little to antigenic stimulation.

4440 ANTIGENIC CHANGES IN CULTURED MURINE LYMPHOMAS AFTER RETRANSPLANTATION INTO SYNGENEIC HOSTS. (Eng.) Cikes, M. (Swiss Inst. Exp. Cancer Res., Lausanne). *J. Natl. Cancer Inst.* 54 (4):903-906; 1975.

Changes of murine leukemia virus (MLV)-determined cell-surface antigen (MV-CSA) and H-2 antigen on reimplantation of cultured murine lymphomas into syngeneic hosts were described. YAC and YCAB lymphomas were induced in an A/Sn(H-2^a/H-2^a) and an (A/Sn x A.CA)F_1 (H-2^a/H-2^f) mouse by inoculation with MLV during the neonatal period. Cell cultures were derived from ascites forms of the lymphomas. Anti-H-2 sera were provided by A.CA anti-A/Sn serum and A/Sn anti-A.SW serum. Anti-MV-CSA serum was produced in (A/Sn x C57BL)F_1 mice by immunization

with ascites YAC lymphoma cells. The reciprocal of the number of cells capable of reducing the cytotoxic potency of the antiserum to 50% was taken as an index of the number of available antigen sites on the cell surface. After retransplantation of cultured YAC lymphoma cells into syngeneic hosts, the antigenic patterns of the cells tended to revert to that characteristic of the *in vivo*-propogated lymphoma lines, as demonstrated by a fourfold increase in H-2 antigen and a 92% decrease of MV-CSA antigen. Similar results were obtained with the YCAB lymphoma line. In addition, a single passage of WLH-1 cultured spontaneous lymphoma cells resulted in almost complete restoration of the H-2 antigen content, and a drastically decreased capacity to absorb anti-MV-CSA serum. Thus reversion to the antigenic pattern characteristic of the corresponding lines propogated *in vivo* was observed, although the mechanisms remain unclear.

4441 SPECIFIC PARTIAL DEPLETION OF GRAFT-*VS*-HOST ACTIVITY BY INCUBATION AND CENTRIFUGATION OF MOUSE SPLEEN CELLS ON ALLOGENEIC SPLEEN CELL MONOLAYERS. (Eng.) Mage, M. G. (Lab. Biochemistry, Natl. Cancer Inst., Bethesda, Md. 20014); McHugh, L. L. *J. Immunol.* 115(4):911-913; 1975.

Spleen cells (from BALB/c mice immunized with the C57BL/6 lymphoma EL4, or from non-immune BALB/c) were incubated on monolayers of [C57BL/6 x BALB/cF_1 (B_6CF_1) spleen cells to investigate the graft-*vs*-host (GVH) reaction. The incubation was carried out for ½ hr or for one hr at 37 C followed by centrifugation for five min at 70 x *g* to 110 x *g* at 34 to 37 C. Control monolayers were BALB/c spleen cells. As measured by the Simonsen spleen weight assay in neonatal mice, GVH activity was partially depleted in cell populations nonadherent to B_6CF_1 monolayers. Residual GVH activity of these nonadherent cells was about half that of cells incubated on the control syngeneic monolayers (the mean of eight experiments was 49% ± 11% S.D.). Two or three consecutive cycles of incubation and centrifugation did not significantly diminished the residual GVH activity. It is suggested that spleen cells with GVH activity are heterogenous with respect to binding to allogeneic target cells under the above conditions. Cell populations non-adherent to third-part [A x AL]F_1 monolayers retained full activity, and cell populations partially depleted of GVH activity in B_6CF_1 neonates had full activity in third-party [BALB/c x AL]F_1 neonates.

4442 SPLENIC REGULATION OF LYMPHOCYTE TRAPPING IN LYMPH NODES DRAINING TUMOR GRAFTS. (Eng.) Fightlin, R. S. (Yale Univ. Sch. Medicine, New Haven, Conn.); Lytton, B.; Gershon, R. K. *J. Immunol.* 115(2):345-350; 1975.

The trapping of chromium-labeled splenic lymphocytes in the lymph nodes and spleens of tumor-inoculated mice was measured. Both histocompatible and incompatible tumors were studied. Methylcholanthrene (MCA)-induced lymphoma, L1210, was inoculated sc into DBA/2 (syngeneic) and C57BL/6 (allogeneic) mice. A BALB/c MCA sarcoma was also injected into histoincompatible C57BL/6 animals. Tumor resections were performed 24 hr before the infusion of 50 μCi ^{51}Cr, at various intervals of tumor growth (1-9 days). The lymph node lymphocytes of the syngeneic animals injected with L1210 exhibited good trapping until the sixth day; after that time they became moribund and died by the ninth day. In the allogeneic animals, the response usually reached a peak at four days, and then declined. The pattern of trapping in popliteal lymph nodes of H2 incompatible animals inoculated with MCA-induced sarcoma was similar to that in the axillary and brachial lymph nodes after L1210 cells were inoculated, except that the peak response did not occur until the 14th day. The splenic trapping response commenced two days after transplantation and abated after a few days. The magnitude of the lymph node trapping response correlated with the magnitude of antigenic difference between tumor and host. Splenectomy two weeks before tumor inoculation had bidirectional effects; it caused a marked augmentation of the trapping response in the early period after tumor inoculation, splenectomized animals trapped less well than intact controls. Tumor resection always led to a rapid fall in the trapping response in intact mice. However, tumor resection at the tumor the time of the peak trapping response of splenectomized mice produced no change. The results indicate that lymphocyte trapping is a valid and useful monitor of the immune response to tumors. They also serve to reemphasize the important regulatory role that the spleen plays in the immune response to tumor-associated antigens by demonstrating a new parameter of splenic control; regulation of lymphocyte traffic in response to antigenic stimuli.

4443 THE HAEMOPOIETIC AND IMMUNOGENIC CAPACITIES OF LIVING HYBRID BONE MARROW CELLS TESTED IN TUMOUR ALLOGRAFT REJECTION. (Eng.) Kerckhaert, J. A. (Dep. Immunol., State Univ. Utrecht, Netherland); Hofhuis, F. M. A.; Willers, J. M. N. *Immunology* 28(4):693-702; 1975.

The hematopoietic and immunogenic capacities of living hybrid bone marrow cells tested in tumor allograft rejections observed in inbred BALB/c mice were investigated. Cell transfer of spleen, bone marrow, lymph nodes, Peyer's patches or thymus cells was performed. Irradiation was obtained by exposing the mice to X-irradiation followed by reconstitution of cells by injecting the cell suspensions into the lateral vein of the tail. All mice received syngeneic or semi-allogeneic bone marrow cells to restore the hemopoietic system. Mice were subjected to treatment with cyclophosphamide injected i.p. IgG2B cells were harvested from ascites, washed with Eagle's medium to be tested for viability by trypan blue exclusion. Tumor assays were determined by s.c. inoculating irradiated mice with tumor cells, followed by examination for the presence of palpable tumors. Lymphoid cells were treated with mitomycin. Hematopoietic and immunogenic capacities of living hybrid bone marrow cells tested in tumor allograft rejections revealed suppression of tumor development after transferral of lymphocytes. Lymph node cells were found to be more active than spleen or thymus cells and bone marrow cells were unable to initiate rejection of the tumor. Mitomycin-treated spleen cells were found to be very effective as an immuno-

gen. Lymph node cells and Peyer's patch cells were also found to be the major cause of the increase in the number of deaths due to anemia. The combining effect of cyclophosphamide treated cells with viable semi-allogeneic cells resulted in an abrogation of the tumor-rejecting capacity. The data support the theory that both semi-allogeneic spleen cells and bone marrow cells are excellent immunogens for histocompatibility antigens.

4444 INDUCTION OF CELL-MEDIATED CYTOTOXICITY, ADULT TOLERANCE, AND ENHANCING ANTISERUM BY 3-M KCL EXTRACT OF TUMOR AND TRANSPLANTATION ANTIGENS. (Eng.) Benjamini, E. (Sch. Medicine, Univ. California, Davis, Calif.); Kharazmi, A. *Transplant. Proc.* 7(1/Suppl. 1):417-421; 1975.

Some immunological properties of 3-M KCl extract of mouse EL-4 leukemia cells of C57BL/6J origin (H-2b) were studied. Ip immunization of BALB/c mice (H-2d) with 37.5 mg of the extract induced the formation of peritoneal exudate cells capable of killing allogeneic tumor cells *in vitro*. The extract (5-10 mg) also induced the formation of antiserum capable of binding with EL-4 cell *in vitro*. The antiserum had the capacity to block the *in vitro* cytotoxic reaction of immune BALB/c peritoneal exudate cells on ^{51}Cr-labeled EL-4 target cells. It also exhibited the capacity to enhance tumor growth and survival when transferred to BALB/c mice transplanted with the allogeneic tumor. In conjunction with cyclophosphamide (1-250 mg/kg), the extract induced tolerance in mice to subsequent transplantation of the allogeneic tumor. The tolerance was expressed by the death of some of the transplanted animals from the allogeneic tumor and by an increase in tumor size and rejection in the remaining animals; by the inability of mesenteric lymph node cells of treated animals to destroy EL-4 target cells; and by the inability of the animals to produce alloantiserum. The duration of the tolerant state was 27 days. The data indicate that the tolerance induced by 3-M KCl extract (in conjunction with cyclophosphamide) is expressed at both the humoral and cellular levels.

4445 REJECTION OF TUMOR CELLS *IN VITRO:* A T-CELL-MEDIATED REACTION. (Eng.) Berczi, I. (Dept. Immunology, Univ. Manitoba, Winnipeg, Manitoba, Canada, R3E 0W3); Sehon, A. H. *Int. J. Cancer* 16(4):665-674; 1975.

A study is presented on the nature and origin of cytotoxic lymphoblastic cells (LBC) formed in cultures of a methylcholanthrene-induced sarcoma (MC-D) of guinea pigs to which normal guinea pig lymphoid cells are added. Normal lymphoid cells were prepared from blood, lymph node, spleen, thymus and bone marrow tissues and suspended in supplemented MEM containing 20% heat-inactivated fetal calf serum. For the induction of LBC, 10^5 MC-D cells/ml were cultured for 24 hr and then 10^7/ml of lymphoid cells were added. Anti-T cell serum was prepared in rabbits immunized with thymus cells of inbred strain 2 guinea pigs. For removal of B-cell antibodies, the anti-thymocyte antiserum was absorbed with homogenized liver, spleen cells and L2C leukemic blood cells until all cytotoxicity for L2C cells was removed. Macrophages for use in tests of macrophage migration inhibition factor in supernatants of MC-D and LBC cultures were obtained from normal guinea pigs administered paraffin oil, ip. It was found in exploratory experiments that LBC were induced by co-cultivation of MC-D with normal lymphoid cells from all sources tested. Foci of LBC were observed on days 4-6 of co-cultivation, which was followed by rapid proliferation of LBC and by the destruction of the tumor cells. Treatment of lymphoid cell preparations with the rabbit anti-T serum prior to co-cultivation with MC-D cells reduced or totally eliminated their ability to develop cytotoxicity. Supernatants of LBC cultures, freed of viable cells by freezing and thawing, inhibited the migration of peritoneal exudate cells, but did not contain lymphotoxic or a skin reactive factor. The absence of the lymphotoxin and skin reactive factor did not, however, militate against the T-cell nature of the LBC since the evidence presently available for liberation of lymphotoxin from guinea-pig lymphocytes is controversial and there is not definite proof of the T-cell origin of these substances. It was concluded that the cytotoxic LBC cells were of T-cell origin.

4446 SELECTIVE SUPPRESSION OF THE IMMUNE RESPONSE EMPLOYING THE GRAFT-VS.-HOST REACTION. (Eng.) Lapp, W. S. (Dept. Physiology, McGill Univ., Montreal, Quebec, Canada); Treiber, W.; Elie, R. *Transplant. Proc.* 7(1/Suppl. 1):393-397; 1975.

Experiments were performed to determine whether graft-*vs*-host (GvH)-induced immunosuppression is due to suppressed T-cell helper function and if GvH mice can develop cell-mediated immunity (CMI) and humoral immunity (HI) after antigenic challenge. Inbred A, CBA, C57BL/6, and various F_1 hybrid mice were used. Normal spleen and thymus cells separated from GvH spleen cells (GvHSC) by a cell-impermeable membrane restored the plaque-forming cell (PFC) response of the GVHSC to SRBC. Treatment of the restoring cells with anti-theta serum prevented the restoration of the PFC response. When GvHSC were used as restoring cells and their adherent cell population removed, they were able to restore the PFC response of responding GvHSC. These results indicated that T-cell helper function is inhibited in GvH mice and that T-cell activity is regulated by an adherent cell population. The antigenic stimulation of CMI and HI was studied in (CBA x A)F_1 mice grafted with C57BL/6 skin 20 days after GvH induction with A strain lymphoid cells. The animals could be induced to reject the skin allografts if challenged with C57BL/6 kidney cells (B6KC) at least once before allografting. However, GvH mice treated with B6KC or with B6KC plus a skin graft followed by a second treatment with B6KC did not produce hemagglutinating antibodies to C57BL/6 antigens. Regardless of their previous treatment, all GvH mice failed to produce PFC in response to SRBC. The selective stimulation of CMI observed in this experiment could serve as a model to study the effect of CMI on tumor growth in the absence of HI.

Preliminary experiments demonstrated that preimmunization of GvH mice with nonviable sarcoma cells markedly retarded tumor growth after subsequent challenge with viable sarcoma cells.

4447 IMMUNOSUPPRESSION BY MURINE LEUKEMIA VIRUSES. (Eng.) Friedman, H. (No affiliation given). In: *Viruses and Immunity: Toward Understanding Viral Immunology and Immunopathology* edited by Koprowski, C., Koprowski, H. New York, Academic Press, Inc., 1975, pp. 17-47.

Recent studies have shown that murine RNA leukemogenic viruses are immunosuppressive. A review of previous work in this area is presented, and some new studies are described. Deficiencies in a variety of antibody responses are consistently observed in leukemia virus-infected mice. The mechanism of such virus induced immunosuppression is, however, not fully understood. Immunosuppression may be due to direct effects of tumor virus infection on different cell types involved in various pathways of the immune response. Studies with a Friend leukemia virus (FLV) model have permitted extensive analyses of various effects of leukemia virus infection on different parameters of antibody formation. Infection of mice with FLV suppresses the primary immune response to SRBC and *Escherichia coli* lipopolysaccharide. Both 19S IgM and 7S IgG hemolysin-forming cells are markedly suppressed in FLV-infected mice challenged with SRBC, with greater depression of the 7S response than 19S response. The time interval between virus infection and challenge immunization, as well as the dose of virus, affected the response. Antigen reactive cells or antibody precursor cells in the B lymphocyte population were the main target for immunosuppression. The numbers of antigen-binding cells for SRBC, both in nonimmune and RBC-immunized mice, were also markedly suppressed. *In vitro* studies indicated that virus-infected leukemic cells, but not cell-free virus, could prevent *in vitro* immunization of normal spleen cells. There was no inhibitory effect on antibody-forming cells directly. Electron microscopy showed the presence of typical leukemia virus particles budding from the surface of many lymphoid cells in the process of secreting antibody to RBC. Thus, leukemia virus infection and antibody formation are not mutually exclusive events at the level of individual immunocompetent cells. FLV infection did not significantly affect the antigen processing mechanism and/or phagocytic cells. A true primary immune response to *Vibrio cholerae* somatic antigen was not affected by FLV infection. In contrast, the secondary immune response to *Vibrio* was readily suppressed, suggesting that antigen-stimulated or antigen-activated immunocompetent cells may be more susceptible to virus infection. The sum total of these studies of the effects of FLV infection on antibody formation indicates that immunosuppression is due mainly to virus-induced alteration of antibody precursor cells *per se*, or alternately, to the preferential infection of antigen-activated lymphoid cells, with a concomitant "autoimmune" response to those cells after they acquired leukemia virus-associated antigens on their surfaces.

4448 EFFECT OF BACILLUS CALMETTE-GUERIN IMMUNIZATION IN MARMOSETS INFECTED EXPERIMENTALLY WITH *HERPESVIRUS SAIMIRI*. (Eng.) Schauf, V. (Rush Presbyt.-St. Luke's Med. Cent., Chicago, Ill.); Fa L.; Deinhardt, F. *Natl. Cancer Inst.* 54(3):721-72 1975.

White-lipped marmosets were immunized with *Bacillus Calmette Guerin* (BCG) in order to determine the effects of BCG immunization on subsequent malignant lymphoma development induced by *Herpesvirus saimiri* (HVS). All but one marmoset developed illness within ten weeks following HVS inoculation. HVS was demonstrated in blood samples of all the animals, as wer HVS-induced early- and late-antigen antibodies. HVS was measured using VERO cell cultures, and HVS anti bodies were measured using indirect immunofluorescence techniques. Lymphocyte reactivity was measure by stimulation of ^{14}C-thymidine uptake. All BCG-immunized marmosets demonstrated delayed hypersensi tivity to tuberculin, indicating that BCG immunization was achieved. No differences were seen between sham- and BCG-immunized groups with respect to the appearance of HVS in blood following inoculation, o set of leukemia, development of serologic responses or deaths due to lymphoma. Average survival time wa slightly longer in BCG-immunized animals, but the effect was not significant. All but one of the 11 H HVS-infected animals died of malignant lymphoma. Th animal that did not, survived 110 days before death One other marmoset survived 100 days with no treatment following HVS inoculation and an additional 10 days when BCG vaccinations were given biweekly. Lymphocyte reactivity to tuberculin induced by BCG was lost following HVS infection. The results indicate that BCG immunization has no effect on the incidence and course of HVS infection in marmosets. The author propose that this may have been due to anergy in HVS infected animals.

4449 BIOLOGIC PROPERTIES OF TRANSPLANTATION IMMUNE SERA. IV. INFLUENCE OF THE COURS OF IMMUNIZATION, DILUTION AND COMPLEXING TO ANTIGEN ON ENHANCING ACTIVITY OF Ig CLASSES. (Eng.) Duc, H. T. (INSERM, Hopital Saint-Antoine, 184, rue du St Antoine, Paris 12, France); Kinsky, R. G.; Kanellopoulos, J.; Voisin, G. A. *J. Immunol.* 115(4):1143-1150; 1975.

The influence of the course of immunization on the enhancing activity of antibody classes was studied by passive enhancement of growth of A/JAX sarcomas (SA 1) in CBA and IC mice and of C57BL leukemia (EL 4) in BALB/c mice. The influence of dilution of antibodies and of complexing to antigens was also studied. Sera were obtained from the mice after immunization and were fractionated by Sephadex-200 chromatography to yield IgM and IgG. The IgG was further fractionated by DEAE-cellulose chromatograph to yield pure IgG2a. IgG1 was obtained from the mor cationic fractions after appropriate immunoabsorption. During repeated immunizing injections of tumo cells, the enhancing capacity of sera increased together with IgG antibody activity as revealed by hemagglutination, cytotoxicity, hemolysis, and direct allogeneic anaphylactic degranulation tests. The

enhancing activity was resistant to mercaptoethanol and showed no correlation with IgM antibody activity. In general, the effects of the IgG were in close agreement with those observed with unfractionated sera. However, in experiments using CI mice and tumor inocula that were low in cell numbers, an inhibitory effect expressed by absence of tumor growth was demonstrated with whole sera and IgG fractions. IgG1 was found to be more enhancing than an equal number of hemagglutinating units of IgG2a. The relative effects of IgG1 and IgG2a were reversed by progressive dilution of the antibodies, the IgG1 activity disappearing and the IgG2 acquiring enhancing properties. These findings appear to provide a basis for understanding certain discrepancies previously reported to exist between findings of the present authors and those of other investigators.

4450 ANALYSIS OF SERA FROM SV40-IMMUNIZED AND TUMOR-BEARING HOSTS FOR BLOCKING ACTIVITY AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY. (Eng.) Lausch, R. N. (Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, Pa. 17033); Sofranko, J.; Prather, S. O. *J. Immunol.* 115(3):682-687; 1975.

The role of serum factors in tumor immunity to cells transformed by PARA-(defective simian virus 40-adenovirus 7 simian virus 40) was investigated. Sera from (SV40)-sensitized hosts did not block the specific cytotoxicity of SV40-sensitized spleen cells for PARA-7 cells. However, such sera could enhance the ability of nonsensitized spleen cells to produce specific killing. This activity could be absorbed out by PARA-7 cells but not by cells transformed by cytomegalovirus. The activity of sera from hamsters bearing tumor isografts depended upon when, after transplantation, the specimens were obtained. Sera collected ten days after grafting or later completely blocked immune spleen cell cytotoxicity and did not mediate target cell killing in the presence of normal spleen cells. Sera obtained at an earlier time, i.e., 3-6 days after transplantation, consistently were active in the antibody-dependent cellular cytotoxicity test and exhibited reduced or no blocking or antibody-independent cellular cytotoxicity. Thus, there appears to be an inverse correlation in the capacity of serum from tumor-bearing hosts to block effector cell cytotoxicity and mediate antibody-dependent cellular cytotoxicity.

4451 EFFECT OF ANTISERA OF DIFFERENT STAGES OF EMBRYOGENESIS ON 22a HEPATOMA ASCITES CELLS AND ON TUMOR DEVELOPMENT IN C3H/Sn LINE MICE. (Rus.) Bronovitskii, A. Iu. (Minsk State Medical Inst., Minsk, U.S.S.R.); Lemeshonok, L. S. *Dokl. Acad. Nauk B.S.S.R.* 19(9):847-850; 1975.

The effect of rabbit sera against embryonal and mature tissues of C3H/Sn line mice, chickens, and against tumor cells on 22a hepatoma ascites cells and on tumor development was studied in C3H/Sn - AG22aC3H line mice. Antisera to tumor cells and to embryonal cells of the early stages of embryogenesis showed the most powerful effect on tumor cells in *in vitro* staining tests. Complete inhibition of tumor growth was observed in mice inoculated with tumor cells incubated with antisera to 11-day-old mouse embryos. The transplantability of ascitic hepatoma was reduced by antisera to 9- and 11-day-old mouse embryos more than by antitumor sera and by antisera to 13-day-old mouse embryos and adult mouse tissues. The duration of the survival of mice inoculated with tumor cells incubated with antisera to 5- and 7-day-old chicken embryos and to 9- and 13-day-old mouse embryos was longer than that of mice which received tumor cells incubated with antisera to 11- and 13-day-old chicken embryos, to 18-day-old mouse embryos, and to tissues of adult mice and chickens. The survival time was the same after incubation of the tumor cells with antisera to 5-day-old chicken embryos, 9- and 13-day-old mouse embryos, or to the tumor. The antiserum to 11-day-old mouse embryo showed a more powerful antitumor effect than the antitumor antiserum. The findings indicate that antisera to mouse and chicken embryos at the early stages of embryogenesis have the highest tumor inhibiting activity, and that these tumor cells acquire certain traits of embryonal cells and tissues of early stages of the embryogenesis.

4452 SERUM ANTI-IMMUNOGLOBULINS IN MULTIPLE MYELOMA AND BENIGN MONOCLONAL GAMMOPATHY. (Eng.) Lindstrom, F. D. (Univ. New Mexico Sch. Med., Albuquerque); Williams, R. C., Jr. *Clin. Immunol. Immunopathol.* 3(4):503-513; 1975.

Sera from 111 patients with immunoglobulin G (IgG) myeloma (MM) and 76 patients with IgG monoclonal gammopathy (BMG) were examined for the presence of anti-IgG antibodies by the method of agglutination of Rh-positive cells coated with various human incomplete Rh antibodies. Definite positive agglutinating reactions were seen in 49.5% of the MM patients compared with 26.3% of the patients with BMG and 28% of 100 age-matched controls. In general, the specificity of the anti-IgG agglutinating activities in most sera appeared to be directed against determinants present in whole human Cohn Fraction II and in some instances Fc, but not present in Fab or $F(ab)_2$. No clear evidence for anti-idiotypic reactivity with autologous M components could be obtained. In most sera, anti-IgG factors appeared to be present in low-molecular weight fractions (3.5-5.0S). The apparent increase in anti-Ig factors in MM as opposed to BMG may reflect a basic difference in control mechanisms. It is possible that tumor-specific antigens produce enhancing antibodies capable of abrogating a cell-mediated immune response of benign plasma cells and encouraging the proliferation of malignant plasma cells.

4453 TRIGGERING MECHANISM OF B LYMPHOCYTES. II. INDUCTION OF ORNITHINE DECARBOXYLASE IN B CELLS BY ANTI-IMMUNOGLOBULIN AND ENHANCING SOLUBLE FACTOR. (Eng.) Watanabe, T. (Osaka Univ. Medical Sch., Fukushima-ku, Osaka, 553, Japan); Kishimoto*, T.; Miyake, T.; Nishizawa, Y.; Inoue, H.; Takeda, Y.; Yamamura, Y. *J. Immunol.* 115(5):1185-1190; 1975.

In vitro stimulation of rabbit lymphocytes with anti-immunoglobulin antibody (anti-Ig) induced

ornithine decarboxylase (ODC) in the cells. The enzyme activity reached the maximum at eight hr after stimulation of the cell with antibody and returned to the unstimulated level after 20 hr. The optimum concentration of antibody to produce the maximum activity of ODC was 25 μg/ml, which was in the same range as that required for the maximum production of IgG and the highest rate of DNA synthesis. ODC was again induced with soluble factor (SF) in the cells that had been previously treated with anti-Ig antibody for 24 hr. The treatment of the cells with anti-thymocyte serum and complement did not affect the activity of the enzyme induced by anti-Ig or by SF, indicating that enzyme induction was an event occurring in B cells and not in T cells. The addition of mitotic inhibitors, such as hydroxyurea (HU) or cytosine arabinoside (Ara-C), to the culture with anti-Ig did not inhibit the production of ODC. The presence of cytochalasin-B with anti-Ig did not inhibit, but rather enhanced, the synthesis of ODC. On the other hand, the presence of HU or cytochalasin-B with soluble factor completely suppressed the induction of ODC. These results suggested that intracellular events that trigger the induction of ODC by the interaction of Ig receptor with anti-Ig may be different from the events that induce the same enzyme triggered by SF.

4454 MULTIPLE INDIVIDUAL AND CROSS-SPECIFIC IDIOTYPES ON 13 LEVAN-BINDING MYELOMA PROTEINS OF BALB/c MICE. (Eng.) Lieberman, R. (Natl. Inst. Allergy and Infectious Diseases, Bethesda, Md. 20014); Potter, M.; Humphrey, W.; Jr.; Mushinski, E. B.; Vrana, M. *J. Exp. Med.* 142(1): 106-119; 1975.

Thirteen levan-binding myeloma proteins (LBMP) of BALB/c origin were classified into two groups with different binding specificities; one group of 11 proteins bound β2→1 fructosans, and a second group of two proteins bound fructosans probably of β2→6 linkage. Anti-idiotypic sera prepared to ten of the proteins in the appropriate strains of mice identified numerous idiotypic determinants. Each protein used for immunization had its own unique individual idiotypic specificities (IdI) and in addition most of the proteins carried 2-9 cross-specific or shared idiotypes (IdX) that were found only among LBMP, and not found in 106 non-LBMP. Most of the IdX determinants and only four of the IdI determinants of the β2→1 fructosan binding group were located in the antigen-binding site. The multiplicity of antigenic differences in this functionally related group of immunoglobulins reveals an unexpected degree of heterogeneity in V-regions that appears to be unrelated to binding.

4455 DIFFERENCES IN SUSCEPTIBILITY OF MATURE AND IMMATURE MOUSE B LYMPHOCYTES TO ANTI-IMMUNOGLOBULIN-INDUCED IMMUNOGLOBULIN SUPPRESSION *IN VITRO*: POSSIBLE IMPLICATIONS FOR B-CELL TOLERANCE TO SELF. (Eng.) Raff, M. C. (Dept. Zoology, University Coll. London, WC1E 6BT, England); Owen, J. J. T.; Cooper, M. D.; Lawton, A. R., III; Megson, M.; Gathings, W. E. *J. Exp. Med.* 142(5):1052-1064; 1975.

Organ explants and dissociated cells from fetal and adult BALB/c mouse lymphoid tissues were used to study the *in vitro* effects of anti-Ig antibodies on developing and mature immunoglobulin M (IgM)-bearing B lymphocytes. Purified goat antibodies against mouse μ-chains and rabbit antibodies against mouse immunoglobulin determinants, and their Fab fragments, inhibited the development of IgM-bearing B cells in explant cultures of 14-day mouse fetal liver, and caused the disappearance of cell surface IgM in explant and dissociated cell cultures of more developed lymphoid tissues. While treatment of cultures of fetal or newborn liver, or adult bone marrow, with low concentrations (<10 μg/ml) of anti-Ig for 24 hr or less caused the complete, but reversible, disappearance (modulation) of cell surface IgM, treatment for 48 hr or more produced irreversible IgM suppression. In contrast, anti-Ig-induced suppression of cell surface IgM in cultures of adult spleen or lymph nodes required much higher concentrations of antibody (≥100 μg/ml) and was always reversible. These differences between immature and mature IgM-bearing cells could not be related to differences in the amount of surface IgM on the cells. The remarkable sensitivity of newly formed B cells to IgM modulation and irreversible IgM suppression when ligands bind to their Ig receptors, may have important implications for B-cell tolerance to self antigens.

4456 DEVELOPMENT AND INHIBITION OF CYTOTOXIC ANTIBODY AGAINST SPONTANEOUS MURINE BREAST CANCER. (Eng.) Stolfi, R. L. (Catholic Med. Cent. Brooklyn Queens, Inc., Woodhaven, N.Y.); Fugmann, R. A.; Stolfi, L. M.; Martin, D. S. *J. Immunol.* 114 (6):1824-1830; 1975.

An investigation was conducted to elucidate the various components and to determine the pattern of humoral immunity in a spontaneous, autochthonous murine breast tumor system. Female (BALB/cfC3H x DBA/8)F_1 hybrid mice (CD_8F_1), infected maternally with mammary tumor virus, or CD_8F_1 male mice bearing a first-generation tumor transplant were used. For the detection of tumor-specific, complement-dependent cytotoxic antibody, reaction conditions were modified to maximize cytolytic complementation with mouse serum. When modified conditions were used, tumor-specific cytotoxic antibody was detected in high dilutions of sera (1:100-1:1000), but not at low dilutions (1:10). Since such a pattern of reactivity suggested the presence of an inhibitor of cytotoxic antibody in high concentrations of serum, further tests were conducted to determine its nature. Sequential measurements subsequent to primary tumor implantation revealed that, although the time of appearance of this inhibitor varied from tumor to tumor, it always became detectable simultaneously with significant levels of lymphocyte-blocking activity, the inhibitor of cytotoxic antibody activity was shown to operate through a competitive antigen-binding and blocking mechanism. These data suggest the possibility that a single serum moiety may be responsible for the efferent blocking of both the cellular and the humoral components of the immune tumor rejection response.

457 ANTIGENS SHARED BY LEUKEMIC BLAST CELL AND LYMPHOBLASTOID CELL LINES DETECTED Y LYMPHOCYTE-DEPENDENT ANTIBODY. (Eng.) Durantez, . (Sch. Medicine, Univ. California, Los Angeles, alif. 90024); Zighelboim, J.; Thieme, T.; Fahey, . L. *Cancer Res.* 35(10):2693-2698; 1975.

he recognition of lymphocyte-dependent antibodies LDA) in numerous heterologous sera led to an nvestigation utilizing an LDA assay system composed y ^{51}Cr-labeled target cell (lymphoblastoid cell ines, acute leukemia blasts, and peripheral blood eukocytes) rabbit antisera against RPMI-4265 as he source of antibodies and peripheral blood eukocytes obtained from adequately selected healthy onors as effector cells. LDA directed against ntigenic determinants present on lymphoblastoid ell lines as well as human leukemia blast cells ere demonstrated in heterologous antisera obtained y immunizing rabbits with a membrane fraction from PMI-4265 (a lymphoblastoid cell line derived from patient with chronic myelogenous leukemia). LDA as present at high titers against B-lymphoblastoid, yelomonocytic, and stem cell lines. The T-lymphoblastoid cell line MOLT-4, however, did not react. DA was demonstrated against acute myelogenous as ell as lymphoblastic leukemia cells. The reactivity as not directed against phytohemagglutinin-induced lastoid antigens, fetal antigens, or fetal calf erum. Absorptions with lymphoblastoid cell lines emoved all LDA reactivity. Similar results were btained by absorbing the rabbit antiserum with cute lymphoblastic and/or acute myelogeneous eukemia cells. These findings indicate the preence of cross-reactive antigens between lymphoblastoid cell lines and leukemia cells. Furthere, cross-reactivity between acute lymphoblastic nd acute myelogenous leukemia cells was demonstrated.

58 A MICRORADIOIMMUNOASSAY FOR ANTIBODIES TO TUMOR-ASSOCIATED ANTIGENS. (Eng.) Huang, C.-C. (Lab. Center for Disease Control, Ottawa, ntario, Canada); Berczi, I.; Froese, G.; Tsay, H. ; Sehon, A. H. *J. Natl. Cancer Inst.* 55(4):879-86; 1975.

versatile rapid microradioimmunoassay for the dection of antibodies to tumor-associated and other ssue antigens is described. The method involves e preparation of solid-phase antigen with cultured lreadу adhered) or noncultured cells (sedimented centrifugation) fixed to Micro-Test plates with eutral buffered formaldehyde or absolute methanol; e incubation of the antigen with test or control era; and the incubation of the antigen with radiodinated antiglobulin antibody. The nonspecific ckground of radioactivity was reduced to an acceptle level by precoating the fixed cells in the wells th 0.5% bovine serum albumin in phosphate-buffered line which was also used for the dilution of sera d labeled antiglobulin antibody. Tumor cells in imary cultures gave a high background, as compared long-term cultures, which was due to the presence immunoglobulins (most likely tumor-specific antidy). The specific antibody response to a syngeneic use tumor was demonstrated by this technique. This thod lends itself to the determination of the kinetics of antibody formation in tumor-bearing hosts and transplant recipients.

4459 DETECTION OF ANTIBODIES TO Ia ANTIGENS IN H-2 ALLOANTISERA. (Eng.) Sachs, D. H. (Natl. Cancer Inst., Bethesda, Md.); Fathman, C. G.; Cone, J. L.; Dickler, H. B. *Transplant. Proc.* 7(1/Suppl. 1):123-126; 1975.

The presence of Ir-associated (Ia) murine cell-surface antigen specificities in H-2 antisera was studied by absorption and testing of antisera on lymphoid cells from H-2-recombinant strains differing genetically only in the Ir region. An H-2 alloantiserum [(B6 x A)F_1 anti-B10.D2], for which recombinants capable of mapping component Ia specificities are not yet available, was examined for its ability to show differential absorptive properties and to block the binding of aggregates to the B-cell Fc receptor. In a fashion analogous to that previously observed with H-2 antisera containing known Ia specificities, absorption of (B6 x A)F_1 anti-B10.D2 antiserum with an Ia-negative ascites tumor removed the reactivity with the tumor but not the reactivity with a subpopulation of normal splenic lymphocytes. As shown by testing of the absorbed antiserum on nylon column-separated spleen cells, the residual cytotoxic activity was directed predominantly against B cells. Preincubation of splenic lymphocytes with the antiserum increased the percentage of cells staining with fluorescent rabbit antimouse immunoglobulin reagent (which detects B-cell surface immunoglobulin), but markedly inhibited the binding of immunoglobulin aggregates to Fc receptors. Lack of complete absorption by the Ia-negative tumor and the ability of the serum to block binding to the Fc receptor both indicate the probable presence of anti-Ia activity with this H-2 antiserum.

4460 SENSITIVITY OF THE EPSTEIN-BARR VIRUS TRANSFORMED HUMAN LYMPHOID CELL LINES TO INTERFERON. (Eng.) Adams, A. (Dept. Tumor Biology, Karolinska Inst., Stockholm 60, Sweden); Strander, H.; Cantell, K. *J. Gen. Virol.* 28(2):207-217; 1975.

The effect of interferon on expression of Epstein-Barr virus (EBV) early gene functions in 14 human EBV-transformed lymphoid cell lines was investigated. The 'early antigen' synthesis which follows either EBV superinfection of established lymphoid cell lines or 5'-iododeoxyuridine activation of the intrinsic EBV genomes harbored by these cells was suppressed with interferon (1, 10, 100, 1000, and 10,000 U/ml, 48 hr). In contrast, the spontaneous early antigen expression that occurs in a few cells in the producer cell lines could not be blocked with interferon. The lymphoid cell lines tested differed in their ability to acquire an antiviral state after exposure to interferon. Several cell lines were also growth inhibited by the interferon preparations. The antiviral and growth inhibitory activities of different interferon preparations could not be separated by a number of criteria. The growth inhibitory activity was nondialysable, nonsedimentable (two hours, 100,000 x *g*), and was destroyed by trypsin

digestion. It also precipitated with interferon when crude WBC interferon preparations were heated at 70 C for one hour, and the antiviral and growth inhibitory activities had the same kinetics of inactivation both at 60 and 75 C. Final proof that the anti-growth substance is interferon itself will require access to interferon purified to homogeneity.

4461 CLINICAL SIGNIFICANCE OF α_2H-GLOBULIN. (Eng.) Yachi, A. (Sapporo Medical Coll., Sapporo, Japan); Akahonai, Y.; Takahashi, A.; Wada, T. *Ann. N.Y. Acad. Sci.* 259:435-445; 1975.

Incidences of α_2H-globulin (α_2H), an iron-containing glycoprotein, in sera of patients with neoplastic and nonneoplastic diseases are reported. Serum α_2H was determined by a counterimmunoelectrophoresis procedure in which an agarose gel plate containing 4% specific anti-α_2H serum was punched out with wells 3 mm in diameter into which 9 µl samples of test serum were introduced. The plate was then subjected to constant current of 2 mA/cm plate width for a running time of about 5 hr. Concentration of α_2H was expressed as an arbitrary unit defined in terms of a 17 mm peak height of precipitate corresponding to 1 U/ml. In the sera of 13 of 37 cases (35%) with histologically proven hepatocellular carcinoma, α_2H was positive. In sera of patients with gastric, pancreatic, colonic, and bronchogenic carcinoma, incidences of α_2H were 8.3-38.5%. The incidence was 93% for patients with acute myelogenous leukemia (AML), and 60% for patients with multiple myeloma. The changes in serum α_2H levels in cases with AML showed increases in stages of relapse, whereas levels decreased in remission following chemotherapy. In chronic myelogenous leukemia, however, only 1 of 7 cases were α_2H-positive, this case being in a stage of acute blastic crisis. In contrast, healthy adult subjects were all α_2H-negative. With regard to cord blood serum, α_2H was detectable in 4 of 42 cases. In nonneoplastic disorders, however, α_2H was positive in sera of 3 out of 5 cases with aplastic anemia. All other cases with various diseases including hepatic, renal, and connective tissue disorders were α_2H-negative. It was not known whether or not serum α_2H is identical with tumor-associated and acidic isoferritin of carcinofetal or carcinoplacental origin.

4462 ANTIGENIC IDENTITY OF ALPHA-MACROFETOPROTEIN AND ACUTE PHASE PROTEIN IN THE RAT. (Eng.) Boss, J. H. (Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel); Dishon, T.; Rosenmann, E. *Biomedicine* 23(6):196-197; 1975.

α-Macrofetoprotein (AMFP) is present in the serum of rat embryos and neonates, pregnant and postpartum females, and hepatoma-bearing animals. Acute phase protein (APP), an alpha-2-AP globulin, occurs in the serum of rats with acute toxic liver injury. The possibility that these proteins might be identical was investigated by cross reacting antisera raised in rabbits against embryonic serum (ES) and against inflammatory serum (IS) from adult male rats injected with turpentine (1 ml, sc and im) 24 hr previously. In Ouchtelony's double immunodiffusion test, the reaction of the anti-ES and anti-IS sera, made specific by absorption pro cedures, with their homologous antisera elicited the formation of two precipitin bands (correspond ing to α-fetoprotein and AMFP) and on precipitation line (corresponding to APP). When the two antisera were reacted with both IS and ES in doub immunodiffusion plates, a single precipitin line, giving a reaction of complete identity, developed between IS and ES. A second line developed betwe ES and its homologus antiserum, corresponding to the α-fetoprotein present in embryonic blood. Th results clearly demonstrate the antigenic identit between AMFP and APP.

4463 α-FETOPROTEIN AND ALBUMIN SYNTHESIS DURING THE CELL CYCLE. (Eng.) Tsukad Y. (Hokkaido Univ. Sch. Medicine, Sapporo, Japan) Hirai, H. *Ann. N.Y. Acad. Sci.* 259:37-44; 1975.

The synthesis of α-fetoprotein (AFP) and albumin in two clones of AH66 hepatoma (C-4 and A-1) was studied. The amount of AFP in culture supernatan was determined by radial immunodiffusion, radioimmunoassay, and incorporation of [^{11}C]leucine in the proteins during *in vitro* incubation (48 hr, 37 C). Amounts of AFP and albumin synthesized by the C-4 clone were 2.9 x 10^{-7} and 0.28 x 10^{-7} µg/cell/hr, respectively. The quantities of AFP and albumin synthesized by the A-1 clone were 2.5 x 10^{-7} and 1.8 x 10^{-7} µg/cell/hr, respectivel The cell cycles of the C-4 clone (mean generation time 20.5 hr) were as follows: G1, ten hours; S, seven hours; G2, four hours; and M, 30 min. For the A-1 clone (mean generation time 50.7 hr), the cycles were as follows: G1, 36 hr; S, ten hours; G2, four hours; and M, 30-60 min. AFP was synthesized from late G1 phase to the end of the S phase for nine hours in C-4, and 25 hr in A-1. The albumin production was from late S phase to the beginning of the G2 phase for four hours in C-4 and nine hours in A-1, which were about half or one-third of the time spent on AFP production. The double staining with fluorescent-conjugated antibodies to AFP and albumin demonstrated that AFP and albumin are probably synthesized by different cells.

4464 ALPHA-FETOPROTEIN PRODUCING CLONES DERIVED FROM ASCITES HEPATOMA AH70B IN CULTURE. (Eng.) Nishina, K. (Okayama Univ. Medical Sch., Okayama, Japan). *Acta Med. Okayama* 29 (1):17-28; 1975.

For convenience in elucidating the biological and biochemical properties of α-fetoprotein (AFP), a rat ascites hepatoma was cultured as a permanent cell line which synthesized AFP at a high level. The ascites tumor from which the cell line was derived was transplantable in Donryu strain rats. Cells from tumor ascites fluid were treated with trypsin to produce a suspension of single cells, and the cells at a concentration of 10^4/ml were grown as primary cultures in Petri dishes in MEM containing 10% heat inactivated bovine serum and 10% fetal calf serum. The primary cultures were

treated with trypsin and subcultured in medium containing 20% heat inactivated bovine serum. Clonal isolation was performed by a method involving the use of trypsinized filter paper. For use in detection of AFP in cultured cells fixed on cover slips, anti-AFP serum was labeled with fluorescein isothiocyanate. The antiserum was prepared in rabbits with the use of a crude AFB preparation obtained by $(NH_4)_2SO_4$ precipitation of serum of tumor-bearing rats, followed by absorption of the antiserum with adult rat serum. For detection of rat serum proteins in culture medium, rabbit antiserum against adult rat serum was prepared by an immunization procedure similar to that used for preparation of anti-AFP serum. Double diffusion and immunoelectrophoresis procedures were used for this purpose and the culture medium was concentrated by ultrafiltration before it was tested for the presence of the rat serum proteins. The cultured cells were found to be morphologically epithelial and to show a mode of chromosome number in the hypotetraploid range. They developed into tumors when backtransplanted ip into adult male Donryu rats. The cells secreted AFP and a few serum proteins into the culture medium for more than one year. AFP was also detected in the cytoplasm of the cultured cells by the fluorescent technique. Six clones which were isolated showed little difference in characteristics. It was suggested, based on the cloning procedure used, that the cultured cells derived from a single cell were secreting both AFP and several components of serum proteins.

4465 MICROHETEROGENEITY OF RAT α-FETOPROTEIN. (Eng.) Watanabe, A. (Okayama Univ. Medical Sch., Okayama, Japan); Taketa, K.; Kosaka, K. *Ann. N.Y. Acad. Sci.* 259:95-108; 1975.

Some physicochemical and immunological properties of microheterogeneous forms of α-fetoprotein were examined in an attempt to elucidate the nature of the observed microheterogenicity. A purified and homogeneous preparation of AFP from pooled fetal rat serum, as judged by both electrophoresis on Cellogel and immunoelectrophoresis, was separated into two components, AFP_a and AFP_b by disc electrophoresis on 7% polyacrylamide gel. These two components had a definite difference in electrostatic net charge and gave only a single band on sodium dodecyl sulfate electrophoresis. Treatment with β-mercaptoethanol (0.5 M) in the presence or absence of 7.5 M urea failed to cause AFP (40 μg) to react with the antiserum, and showed a broad band with slower migration. Mercuric chloride (33 mM) and 33 mM N-ethylmaleimide caused the separation of AFP_a and AFP_b to be obscured. No alteration in electrophoretic or immunological properties of AFP was observed upon treatment with 7.5 M urea or 0.33 M guanidine hydrochloride. Electrophoresis of neuraminidase-treated (six hours) AFP (20 μg) on 5% polyacrylamide gel yielded clearly separable, slower moving four to six and finally two components depending on the time of incubation (2,6 min; 3,6 hr; 4,12 hr) with neuraminidase. The time-dependent conversion of faster into slower migrating components of both AFP_a and AFP_b upon neuraminidase treatment was confirmed by reelectrophoresis of separated and similarly treated AFP_a and AFP_b. Two bands of sialized or desialized AFP were also observed on isoelectric focusing. Both AFP_a and AFP_b treated with and without neuraminidase gave single fused precipitin lines against the antiserum in Ouchterlony double-diffusion analysis. On the basis of the changes in electrophoresis mobilities of the intermediates following neuraminidase treatment, AFP_a and AFP_b were estimated to have at least 2.5 and 4.5 molecules of sialic acid per molecule, respectively.

4466 EVOLUTION OF α-FETOPROTEIN SERUM LEVELS THROUGHOUT LIFE IN HUMANS AND RATS, AND DURING PREGNANCY IN THE RAT. (Eng.) Masseyeff, R. (Faculte de Medicine, Nice, France); Gilli, J.; Krebs, B.; Calluaud, A.; Bonet, C. *Ann. N.Y. Acad. Sci.* 259:17-28; 1975.

The evolution of serum α-fetoprotein (AFP) levels in man and rat was studied throughout the life span, using a radioimmunoassay method (RIA) with specific antisera for human and rat AFP, respectively. Sera of 201 clinically normal children, 192 healthy adult blood donors, and 16 individuals aged 70-98 were assayed. Sera of 66 Sprague-Dawley rats aged 3-70 wk were also assayed. In man, AFP levels decreased steeply during the first year and reached a low basal range by the end of the second year. This low basal range was maintained throughout adult life. The rat showed a similar pattern, although at a higher concentration at every stage. A difference between these two species was that puberty occurred while AFP was still decreasing in the rat, whereas in many, the adult basal level was achieved long before the onset of puberty. In both species the normal range was more scattered during the beginning of life than it was thereafter. The evolution of maternal serum AFP was also studied in 29 Sprague-Dawley pregnant rats. AFP levels began to increase sharply on the 10th-13th day of pregnancy. From the 13th to the 19th day a deceleration of AFP increase was observed that led to a decrease between the 17th and 19th day. From the 19th to the 21st day AFP levels again increased steeply. A significant correlation was observed on the 21st day of pregnancy between the number of fetuses of the progeny and the maternal level of AFP. A reduction of the AFP level occurred following hemihysterectomy that was grossly proportional to the number of remaining fetuses. The persistance of a stable level during adult life can be explained solely by the stability of the synthesis of this protein. Conversely, in pregnancy the evolution of the serum AFP curve is dependent of the fetal synthesis, maternal and fetal catabolism, and permeability of the placental barrier.

4467 α-FETOPROTEIN LEVELS IN NORMAL MALES FROM SEVEN ETHNIC GROUPS WITH DIFFERENT HEPATOCELLULAR CARCINOMA RISKS. (Eng.) Sizaret, P. (International Agency for Res. on Cancer, 69008 Lyon, France); Tuyns, A.; Martel, N.; Jouvenceaux, A.; Levin, A.; Ong, Y. W.; Rive, J. *Ann. NY Acad. Sci.* 259:136-155; 1975.

α-Fetoprotein (AFP) levels of 1,335 men (15 yr and older) of seven ethnic groups (Chinese, Indians, and Malays from Singapore, Caucasians from Lyon, and Negroes from Nairobi, forest, and the savanna region of the Ivory Coast) were determined by radioimmunoassay. These levels were obtained in an attempt to correlate AFP with hepatocellular carcinoma (HCC) risk. A few elevated levels (up to 30 nU/ml) were detected in some normal individuals, especially in the older age-groups. There was a systematic age-dependency of AFP levels particularly evident in the groups from Singapore-Lyon, in which there was a 50% AFP increase between the ages of 20 and 40. Comparison between Africans on the one hand and people from Singapore-Lyon on the other hand revealed highly significant differences ($p < 0.001$), especially in the younger groups, whereas Chinese, Malays, and Indians from Singapore had very similar AFP patterns; this suggests an important role for environmental factors in the regulation of AFP levels. The age dependency of the presumed effect of environmental factors is in keeping with previous data showing that young animals respond more vigorously to AFP-stimulating factors. Although the incidence of HCC differs in the three Singapore groups (the highest in Chinese and the lowest in Indians), no relationship was observed here between mean AFP level and HCC incidence in Singapore.

4468 EARLY DETECTION OF HEPATOMA: PROSPECTIVE STUDY IN LIVER CIRRHOSIS USING PASSIVE HEMAGGLUTINATION AND THE RADIOIMMUNOASSAY. (Eng.) Lehmann, F.-G. (Dept. Medicine, Univ. Marburg, Marburg/Lahn, West Germany). *Ann. NY Acad. Sci.* 259: 196-210; 1975.

A prospective study of serum α-fetoprotein (AFP) elevation in patients with liver cirrhosis was carried out, and the results were compared with clinical conditions and biochemical parameters (SGOT, SGPT, bilirubin, prothrombin complex time, and γ-globulin). The possibility was also investigated of a general screening of patients with precancerous disease. The passive hemagglutination method involved the use of SRBC to which rabbit IgG antibody prepared against crystalline human AFP was bound with bis-diazotized benzidine. The radioimmunoassay was carried out with ^{125}I-labeled AFP in a double antibody technique using anti-AFP serum from the rabbit as the first antibody and anti-rabbit-γ-globulin serum from the goat as second antibody. Double diffusion and electroimmunoosmophoresis tests were also carried out. The study included 215 patients with liver cirrhosis, of which 165 showed negative results in all four tests. Thirty-one patients of this group died during the study, and were found on autopsy to have liver cirrhosis without carcinoma. Three out of the 215 patients showed positive results in all four tests. The three patients revealed primary liver cell carcinomas. Forty-seven out of the 215 patients yielded negative results by the less sensitive double diffusion and electroimmunoosmophoresis tests, but positive results in the sensitive passive hemagglutination and radioimmunoassay tests. In approximately 90% of the cases, a temporary rise of AFP up to 2,000 ng/ml was not associated with tumor growth at the time of measurement. There was no correlation of AFP level with actual liver dystrophy as determined by the various biochemical parameters. Primary liver cell carcinoma was found to be more frequent in post-hepatitic than in postalcoholic, cryptogenic, and other cirrhosis, and to be more frequent in Australia-antigen positive cases than in Australia-antigen negative cases. Routine serological tumor antigen screening of patients with a precancerous disease is considered to be useful.

4469 SERUM ALPHA-FETOPROTEIN AND BETA-HUMAN CHORIONIC GONADOTROPIN LEVELS IN PATIENTS WITH NON-SEMINOMATOUS GERM CELL TESTICULAR CANCER. (Eng.) Lange, P. H. (Univ. Minnesota, Coll. Health Sciences, Minneapolis, Minn.); Hakala, T. R.; Fraley, E. E. *Minn. Med.* 58(11):813-815; 1975.

Sera from 146 patients with genito-urinary disease were assayed for the presence of alpha fetoprotein (AFP) and beta human chorionic gonadotropin (B-HCG) by recently developed radioimmune assays. Elevated AFP values were found only in patients with non-seminomatous germ cell tumors of the testicle (12/22). B-HCG elevation was present in hypernephroma (3/50), transitional cell carcinoma (3/46), and in testicular tumor patients (12/22), but the levels were greater than 10 mIU/ml in the latter group only. Of 15 sera tested both by gel-agar precipitation and radioimmune assay, ten had elevated AFP values by radioimmune assay, whereas only three were positive by the conventional method. The use of these new serum assays for AFP and B-HCG may have broad applications, both to the diagnosis and management of certain testicular neoplasms.

4470 HUMAN α-FETOPROTEIN IMMUNOCHEMICAL ANALYSIS OF ISOPROTEINS. (Eng.) Alpert, E. (Harvard Medical Sch., Boston, Mass. 02114); Perencevich, R. C. *Ann. N.Y. Acad. Sci.* 259:131-135; 1975.

The basis for separation of human α-fetoprotein (AFP) into two bands during isoelectric focusing was studied. Resolution of the isoproteins into a more uniform band after neuraminidase treatment suggested that the presence of terminal sialic acids contributed to heterogeneity. Staining of the gels after immunofixation with specific antibody suggests that there may be quantitative or qualitative differences in the antigenic determinants of one of the isoproteins. The existence of AFP isoproteins may explain the wide variation found in AFP standards and serum concentrations.

4471 PLASMA LEVELS OF CARCINOEMBRYONIC ANTIGEN IN BRONCHIAL CARCINOMA AND CHRONIC BRONCHITIS. (Eng.) Pauwels, R. (Academic Hosp., State Univ., Ghent, Belgium); van der Straeten, M. *Thorax* 30(5):560-562; 1975.

To determine the clinical value of plasma carcinoembryonic antigen (CEA) in bronchial carcinoma and also whether plasma CEA levels could be used to

discriminate between bronchial carcinoma and other pulmonary disorders, a comparative study was carried out on 49 patients with bronchial carcinoma and 25 patients with acute exacerbation of chronic bronchitis. Using a previously established level of 2.5 ng/ml as the upper limit of normal plasma CEA, an increase was found in 80% of the patients with bronchial carcinoma and in 68% of those with acute exacerbation of chronic bronchitis. Further, there was no statistically significant difference between the two groups. The CEA levels of the patients who died during a 1-yr follow-up were not significantly different from those of the survivors, nor was there any difference in levels of patients who proved to be operable. In addition, there was no correlation between initial CEA level and survival time in patients who died. For the chronic bronchitis patients, no significant lowering of CEA level was observed following response of their acute exacerbation to treatment. It is concluded that a single determination of the plasma CEA level has no prognostic value in patients with bronchial carcinoma, although the possibility is suggested that repeated measurements of CEA levels during follow-up and treatment might have some prognostic significance.

4472 DEMONSTRATION OF TWO MOLECULAR VARIANTS OF CARCINOEMBRYONIC ANTIGEN BY CONCANAVALIN A SEPHAROSE AFFINITY CHROMATOGRAPHY. (Eng.) Harvey, S. R. (Dept. Clinical Chemistry, Roswell Park Memorial Inst., Buffalo, N.Y. 14263); Chu, T. M. *Cancer Res.* 35(11/Part I):3001-3007; 1975.

The carcinoembryonic antigen (CEA) active glycoproteins from perchloric acid extract of liver metastasized primary colon tumor were separated by concanavalin A Sepharose (Con A Sepharose) chromatography. The CEA activities separated by Con A Sepharose chromatography were designated as loosely bound and tightly bound which, respectively, eluted on the Con A Sepharose column between 0.12 and 0.15 M and 0.3 M α-methylmannose in a linear gradient of α-methylmannose. Further purification of these activities by Sephadex G-200, Bio-Gels A-1.5m and P-300 yielded two variants of glycoproteins (B_1 and C_2) with CEA activity. Both purified preparations of CEA had similar immunochemical properties. Their A_{280}/A_{260} ratios were 1.30 and 1.56, respectively. The purified loosely bound CEA(B_1) had immunological, chromatographic, and electrophoretic properties similar to those of ^{125}I-CEA, whereas the tightly bound CEA (C_2) had a lower molecular weight (120,000 - 140,000). Further, specificity of these two CEAs was established by their reactions in immunoelectrophoresis with preparations of specific goat anti-CEA antiserum. The results indicate the practical use of Con A Sepharose affinity chromatography for the separation and characterization of glycoprotein tumor antigens.

4473 IMMUNOLOGICAL AND CHEMICAL STUDIES ON SUB-FRACTIONS OF CARCINOEMBRYONIC ANTIGEN. (Eng.) Rogers, G. T. (Charing Cross Hosp., London W6 8RF, England); Searle, F.; Wass, M. *Immunochemistry* 12(10):839-842; 1975.

For studies on immunological and chemical properties of three components of carcinoembryonic antigen (CEA), the antigen was extracted from liver metastases of colonic tumor tissue with perchloric acid and purified by chromatography on Sepharose 4B and Sephadex G-200. It was then fractionated on a column of concanavalin A Sepharose to give unbound fraction 1, 2% methyl glucoside elutable fraction 2, and 10% methyl glucoside elutable fraction 3. The recovery of protein in each fraction was 10, 50 and 20%, respectively. To test the effect of removal of sialic acid on the fractionation, CEA was also treated with neuraminidase. Rabbit antisera were prepared against unfractionated CEA and fraction 2 and were absorbed with normal colon, spleen, and human plasma before use in double diffusion studies. Established antisera which were monospecific for CEA-unique antigen A were obtained by donation. Circular dichroism spectra were measured on a Cary 61 recording spectropolarimeter. Results of the double diffusion tests showed that each fraction reacted with the established anti-A antisera and also with antisera specific for a determinant, C, common to both CEA and a glycoprotein of normal tissues. Removal of sialic acid from CEA appeared to have no effect on its fractionation on concanavalin A Sepharose or on its binding to antibody. Further, the presence of concanavalin A up to a 40-fold excess did not inhibit the binding of CEA to antibody. These results suggest that con A binding sites are unlikely to be exposed by removal of sialic acid. Results of carbohydrate analyses showed differences in the three subfractions with respect to content of neutral sugar, galactose, fucose, hexosamine, and sialic acid. Results of circular dichroism studies also indicated the existence of chemical differences.

4474 IMMUNOPATHOLOGICAL STUDIES ON CEA AND CEA-ASSOCIATED ANTIGENS WITH REEVALUATION OF THE CANCER SPECIFICITIES OF CEA. (Eng.) Mori, T. (Osaka Univ. Medical Sch., Osaka, Japan); Wakumoto, H.; Shimano, T.; Lee, P.-K.; Higashi, H. *Ann. N.Y. Acad. Sci.* 259:412-416; 1975.

The distribution of targets to anti-carcinoembryonic antigen (CEA) produced in guinea pigs, was studied in 228 surgical specimens. Four antibodies, anti-CEAf_1 (fecal antigen), anti-CEAgc (reacting with gastric and colonic cancer), anti-CEAg (gastric cancer only) and anti-CEAf_2 (from a patient with advanced gastric cancer) were used. CEAgc was detected in 52 of 84 gastric cancers, all of 14 colo-rectal cancers, 1 of 4 pancreatic cancers, as well as in atypical glands of the digestive organs. None of the examined tissues from other organs fluoresced with anti-CEAgc. Atypical glands in the stomach with positive CEAgc showed intestinal metaplasia, but not *vice versa*. Differentiated or mucinous cancers of the stomach were mostly CEA-positive. Atypical glands with CEAgc in the colon were often observed in ulcerative and granulomatous colitis, in polyps, and in areas bordering on cancers. Anti-CEAg showed fairly good reactivity to gastric cancer. The CEA in adenocarcinoma of organs other than digestive system was a CEA-associated fecal antigen. The CEA in squamous cell carcinoma of the endodermal organs was a different CEA-associated fecal antigen. CEA was detected exclusively in adenocarcinoma and

atypical glands of the digestive organs. Minor antigenic differences of CEA among gastric cancer, colonic cancer, and atypical glands were demonstrated.

4475 EMBRYONAL ANTIGEN OF HAMSTER ADENOVIRUS SARCOMA. (Rus.) Bashkaev, I. S. (The P. A. Herzen Res. Inst. of Oncology, Moscow, USSR); Ageenko, A. I. *Vopr. Onkol.* 21(6):93-96; 1975.

Sarcomas induced in hamster by human adenovirus type 12 were investigated for the presence of embryonal antigen. Sarcoma type A-12, induced by the introduction of human adenovirus type 12 into newborn hamsters, sarcoma type A-12, transplanted into adult hamsters, and sarcomas induced in hamsters by the introduction of cell suspensions from lungs without macroscopically visible metastases of sarcoma A-12-bearing animals were used for the experiments. The embryonal tissue was taken from pregnant hamsters between the 10th and 13th days of pregnancy. Embryonal antigen was detected in 50% of both primary and transplanted A-12 sarcomas. This antigen was identical with one of the embryonal antigens detected in the embryonal extract with antiembryonal serum. This embryonal antigen was not present in tumors induced with lung cell suspensions from tumor-bearing animals. The embryonal antigen was found to be serologically identical with the second type of lung tissue antigen that is detectable by sarcoma A-12-specific serum. Consequently, this antigen is also present in the hamster lung. The tissue protein that is serologically identical with the embryonal antigen is apparently increased in the adenovirus-induced tumor. Since this antigen is specific for the embryon, and partly also for the tumor, it may be regarded as a carcinofetal antigen. The negative reaction with the antiembryonal serum in 50% of the A-12 sarcomas tested is apparently due to the low concentration of the embryonal antigen in these tumors.

4476 INVESTIGATION OF SPECIFIC ANTIGENS IN PROSTATIC CANCER. (Eng.) Moncure, C. W. (Medical Coll. Virginia, Virginia Commonwealth Univ., Richmond, Va. 23219); Johnston, C. L., Jr.; Koontz, W. W., Jr.; Smith, M. J. V. *Cancer Chemother. Rep. (Part 1)* 59(1):105-110; 1975.

New Zealand white rabbits immunized with normal human prostatic homogenates (0.5 ml/week for 16 wk, sc) have been shown to develop antibodies specific for one form of prostatic acid phosphatase and a protein antigen which does not appear to possess enzymatic activity. Antibodies were also developed against several other proteins, esterase, two aminopeptidases, and a second form of acid phosphatase. Extensive absorption of the antisera with gluteraldehydepolymerized serum and kidney homogenate removed all antibodies except those which react with the specific acid phosphatase and the specific protein. These two antigens have been separated from each other by ion-exchange chromatography. The partially purified acid phosphatase has been used to produce antiserum employed for the detection of prostatic cancer in bone marrow aspirates. Four patients with known stage IV prostatic cancer were positive by comparative immunodiffusion for prostatic acid phosphatase although no tumor cells were found in the marrow. Positive immunodiffusion reactions have not been seen in any patient without stage IV disease. The identification of prostate-specific substances should provide a rational approach for the development of new diagnostic, prognostic, and therapeutic procedures.

4477 DISTRIBUTION OF FIBROBLAST SURFACE ANTIGEN IN THE DEVELOPING CHICK EMBRYO. (Eng.) Linder, E. (Dept. Serology and Bacteriology, Univ. Helsinki, Helsinki 29, Finland); Vaheri, A.; Ruoslahti E.; Wartiovaara, J. *J. Exp. Med.* 142(1):41-49; 1975.

Fibroblast surface (SF) antigen is present in fibrillar surface structures of cultured normal fibroblasts shed to the extracellular medium, and is also found in circulation (serum and plasma). Malignant fibroblasts (transformed by viruses) do not express SF antigen on the cell surface. In this study, the *in vivo* differentiation and distribution of SF antigen was investigated in the developing chick embryo using cryostat sections and immunofluorescence. The major findings were: *(a)* SF antigen was detectable in the loose connective tissue of very early (two-to three-day old) embryos. *(b)* Condensation of SF antigen was seen in various boundary membranes such as glomerular and tubular basement membranes of the kidney, the boundary membranes of the notochord, yolk sac, and vitelline membranes and liver sinusoids. *(c)* SF antigen was found to be cell-type specific. It was seen as a fibrillar network in the loose connective tissue of different organs but not in the parenchymal cells. It was not found in muscle cells at any stage of development. *(d)* The antigen was present in the undifferentiated mesenchymal cells of the kidney, but not found after their development in epithelial cells of the secretory tubules. *(e)* Both *in vivo* and in fibroblast cultures SF antigen was distributed as a fibrillar network. These data indicate that SF antigen is a "differentiation antigen" restricted to certain cells of mesenchymal origin and character, and that it accumulates in the connective tissue during embryogenesis.

4478 IMMUNOLOGIC STUDY OF ANTIGENS AND MOLECULAR HYBRIDIZATION OF NUCLEIC ACIDS FROM MILK OF BREAST CANCER PATIENTS. (Eng.) Kryukova, I. N. (D. I. Ivanovsky Inst. Virology, Inst. Stomatology, Moscow, U.S.S.R.); Ilyin, K. V.; Mazurenko, N. N.; Vasilevskaya, L. N.; Zhdanov, V. M. *Neoplasma* 22(3):235-241; 1975.

Experiments were carried out in an effort to demonstrate relationships between HEp-2 virus and ultrasediments of milk from lactating mammary carcinoma patients. A rabbit immune serum was prepared against HEp-2 virus and was freed of antibodies against human cell, human serum, and bovine serum antigens. Another rabbit immune serum was prepared against the milk ultrasediment and was freed of antibodies against human species, serum, and embryonic antigens. Precipitin lines in gel diffusion assays were intensified by an autoradio-

graphic method. The studies showed that by the gel diffusion assay both anti-HEp-2 virus serum and anti-breast milk ultrasediment serum precipitated an identical antigen in specimens of milk from mammary carcinoma patients, normal controls, and other controls. This antigen was not identical, however, with the group specific antigen of the HEp-2 virus. At the same time, the anti-breast cancer milk serum did not precipitate the HEp-2 virus. However, molecular hybridization experiments using RNA preparations from milk and ^{3}H-labeled single-stranded DNA from HEp-2 virus revealed nucleotide sequences homologous to nucleic acids of oncornavirus of D-type in milk from breast carcinoma patients as well as in milk from healthy controls.

4479 DELAYED CUTANEOUS HYPERSENSITIVITY REACTIONS TO MELANOMA ANTIGEN. (Eng.) Holmes, E. C. (Dept. Surgery, Univ. California, Los Angeles, Calif. 90024); Roth, J. A.; Morton, D. L. *Surgery* 78(2):160-164; 1975.

Soluble melanoma antigens prepared by 3M KCl extraction were tested by delayed cutaneous hypersensitivity reactions (DCHR) in 52 patients. Maximum reactivity was noted at 24 hr following id injection of the antigen. DCHR was greater than or equal to 10 mm of induration in 20 of 34 cutaneous melanoma patients, whereas only three reacted to an autologous muscle extract. Five of 18 patients with other tumors reacted to this antigen. The availability of soluble tumor antigens now permits further purification, chemical characterization, and clinical evaluation of these antigens.

4480 IMMUNOBIOLOGICAL ROLE OF ALLOANTIGENS OF TISSUE COMPATIBILITY OF THE HOST IN THE STRUCTURE OF ONCORNAVIRUSES. (Rus.) Klepikov, N. N. (Inst. Exper. Path. Ther., Acad. Med. Sci. U.S.S.R., Sukhumi, U.S.S.R.); Khagundokova, L. B. *Dokl. Akad. Nauk. S.S.S.R.* 222(2):466-467; 1975.

The immunological role of tissue compatibility alloantigens of the host with respect to oncornavirus was studied by a virus neutralization test on blood sera from BALB/c mice infected with (Rauscher-D) virus and C3HA line mice infected with Rauscher-K virus. In addition, BALB/c mice were immunized with H-2^k antigen, and were then infected with Rauscher-D and Rauscher-K virus strains. At a dilution of 1:5, the immune serum of the host against H-2^k exhibited a considerable virus neutralizing activity with respect to Rauscher-K, reducing the number of the colonies formed by 76% compared to the control. The same serum showed no noteworthy virus-neutralizing activity against Rauscher-D. Analogous findings were obtained on BALB/c mice immunized with H-2^k antigens. The infectivity of Rauscher-K was reduced by 87% in immunized mice, while there was no change in the activity of Rauscher-D. The findings indicate that the host tissue compatibility antigen antibodies, localized on the outer shell of Rauscher virus, neutralize the infective activity of the virus. The active immunization of the animals with alloantigens of the tissue compatibility of the host may increase their resistance to oncornavirus infection.

4481 THE OCCURRENCE OF THE HL-B ALLOANTIGENS ON THE CELLS OF UNCLASSIFIED ACUTE LYMPHOBLASTIC LEUKEMIAS. (Eng.) Fu, S. M. (Rockefeller Univ. New York, N.Y. 10021); Winchester, R. J.; Kunkel, H. G. *J. Exp. Med.* 142(5):1334-1338; 1975.

The application of B-cell markers from pregnancy sera to the classification of leukemia is described. Six cases of acute lymphoblastic leukemia (ALL) were studied by T- and B-cell membrane markers. Cases with a high percentage of peripheral lymphoblasts were selected. In cases A and B, 98-99% of the lymphoblasts formed rosettes with sheep RBC; these lymphoblasts had neither surface immunoglobulin (Ig) nor the Fc receptors. In the remaining four cases (C-F), the lymphoblasts had no detectable surface Ig of classes δ, μ, γ, α, κ, and λ. In cases E and F, only 60% and 41% of the mononucleated cells were blasts. These blasts did not form E rosettes, whereas a substantial percentage of the small lymphocytes did. Indirect fluorescent studies with HL-B-specific pregnancy sera were performed. In cases A and B, no significant numbers of the lymphoblasts stained with any of the sera. In case C, two of the four sera used stained practically all the lymphoblasts while one stained only 20% and the other stained less than 2%. A similar staining pattern was shown in case D. In cases E and F, the 57% and 36% of cells stained by a pregnancy serum represented the staining of the majority of lymphoblasts in the peripheral blood of these cases. Cases A and B appear to be T-cell leukemias. The detection of Ia-related HL-B antigens on the cells from cases C-F indicate that these cases may be of B-cell lineage.

4482 HL-A IN HODGKIN'S DISEASE. III. A PROSPECTIVE STUDY. *(Eng.)* Kissmeyer-Nielsen, F. (Univ. Hosp., Copenhagen, Denmark), Kjerbye, K. E.; Lamm, L. U. *Transplant Rev.* 22:168-174, 1975.

A prospective study was performed by HL-A typing of all new patients included in the Danish Hodgkin project, LYGRA, and the results were compared to those of previous studies. All 201 patients (80 women and 121 men) followed the same protocol concerning diagnosis and treatment. The control material consisted of 562 normal caucasian blood donors which were randomly HL-A typed. The frequency of the majority of HL-A antigens was similar to the control sample; the most deviating of the HL-A antigens was HL-A1, involving a 10% increase in patients as compared to the controls. The results did not confirm previous findings in two independent series of patients and did not support the increase of other HL-A antigens. One explanation for the discrepancies is that the prospective nature of this study accounts for the differences from the previously published mixtures of prospective and retrospective cases. Twenty-six patients dying from malignant diseases showed a decreased frequency of antigens as compared to an increase in these antigens found in previous retrospective studies. The authors conclude that HL-A1 is increased in patients acquiring Hodgkin's disease, although the relative risk is only slightly increased (1.53) and that there seems to be an as-

sociation between HL-A1 and HL-A9 and sex, age of onset, and histology.

4483 LYMPHOCYTE-ASSOCIATED ANTIGENS IN PATIENTS WITH ALVEOLAR CELL CARCINOMA. (Eng.) Mohr, J. A. (Veterans Admin. Hosp., 921 N.E. 13 St., Oklahoma City, Okla.); Nordquist, R. E.; Coalson, R. E.; Rhoades, E. R.; Coalson, J. J. J. Lab. Clin. Med. 86(3):490-493; 1975.

Antiserum produced in rabbits against a virus-like particle pellet recovered from human alveolar cell carcinoma (AOC) was used for the detection of lymphocyte-associated antigen in patients with AOC. The method used was direct immunofluorescence. Five of 11 patients with AOC demonstrated bright fluorescence, with each having 7-12% total fluorescing lymphocytes. All five of these patients had widespread pulmonary AOC and/or metastatic disease, while the six AOC patients without fluorescence had localized pulmonary AOC. None of the other test subjects (35 healthy subjects, 74 patients with malignancies other than AOC, 30 patients with nonmalignant disease, and seven patients with lupus nephritis) had any cells that fluoresced. The results demonstrate that lymphocytes from some patients with AOC possess antigen and the presence of lymphocyte fluorescence in patients with AOC suggests widespread or metastatic disease. The presence of antigen may be of both diagnostic and prognostic value.

4484 EXTRACTION OF TUMOR-SPECIFIC ANTIGEN FROM CELLS AND PLASMA MEMBRANES OF LINE-10 HEPATOMA. (Eng.) Leonard, E. J. (Natl. Cancer Inst., Bethesda, Md. 20014); Richardson, A. E.; Hardy, A. S.; Rapp, H. J. J. Natl. Cancer Inst. 55(1):73-79; 1975.

The properties of tumor-specific antigen from line-10 ascites variants of diethylnitrosamine-induced hepatoma were studied. Tumor-specific antigen was extracted with 3 M KCl from line-10 guinea pig hepatoma cells. The yield of antigenic activity, estimated by production of delayed cutaneous hypersensitivity reactions in line-10 immune guinea pig, was 10-30% of the antigen present in intact cells. By ultracentrifugation criteria, the extracted antigen was soluble. Gel filtration, ion exchange chromatography, and salting-out studies showed that the antigen was heterogeneous in size and net charge. The possibility that 3 M KCl extracted a homogeneous population of molecules associating into polymers of various sizes at low ionic strength was ruled out by heterogeneity on Sephadex G-200 chromatography at high ionic strength. After osmotic lysis of sucrose-loaded line-10 cells, whole plasma membranes or large membrane fragments were obtained in a yield of about 20%. The isolation procedure did not cause detectable loss of membrane antigenic activity. The membranes had 33 skin test U/mg membrane protein, compared to the intact cell value of 1.7 skin test U/mg cell protein. Extracts of plasma membranes had 10-20% of the antigenic activity of the starting membrane material. In contrast to the wide variety of proteins liberated from intact cells, much of the protein extracted from the membranes was in the molecular wt range above 150,000.

4485 TUMOUR-SPECIFIC ANTIGEN RELATED TO RAT HISTOCOMPATIBILITY ANTIGENS. (Eng.) Bo[illegible]wen, J. G. (Lab. for Experimental Surgery, Erasmus Univ., Rotterdam, The Netherlands); Baldwin, R. W. Nature 258(5530):75-76; 1975.

A tumor-specific antigen preparation isolated from the serum of Wistar rats bearing transplants of a 4-dimethylaminoazobenzene-induced hepatoma (D23) was used to test the hypothesis that tumor-associated antigens (TAAs) of chemically induced tumors are modified histocompatability antigens. Antisera against highly purified hepatoma D23 antigen were raised in New Zealand white rabbits and Sloanaker rats and were tested by the indirect membrane immunofluorescence test for the presence of antibody directed against the tumor-specific antigen on viable D23 cells. The antisera reacted not only against D23 cells but also against two immunologically distinct hepatomas, D30 and D33, indicating that the sera recognized antigenic similarities between the three tumors. After absorption *in vitro* and *in vivo* with normal Wistar liver membranes, the antisera retained their reactivity against D23 but lost their reactivity against D30 and D33. The possibility that hepatoma D23 antigen is a modified histocompatability antigen was further explored by examining the binding of ^{125}I-labeled D23 antigen to columns of immunoabsorbents prepared from Sloanaker antinormal Wistar liver antiserum, normal Sloanaker serum, Wistar antihepatoma D30 antiserum, and Wistar antihepatoma D23 serum. Results of the binding assay showed that D23 antigen has points of identity with antigens recognized by Sloanaker rats on normal Wistar liver membranes. This work confirms that the hepatoma D23 antigen is a modified histocompatability antigen.

4486 LYMPHOCYTE RESPONSE TO AUTOLOGOUS TUMOR ANTIGEN(S) AND PHYTOHEMAGGLUTININ IN OVARIAN CANCER PATIENTS. (Eng.) Chatterjee, M. (Gynecology Dept., Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14203); Barlow, J. J.; Allen, E. J.; Chung, W. S.; Piver, M. S. Cancer 36(3):956-962; 1975.

The response of lymphocytes from 11 patients with ovarian carcinoma to autologous tumor antigens and phytohemagglutinin (PHA) was studied. Lymphocytes from age matched normal women served as controls. Tumor antigen was prepared by homogenizing tumor tissue, and immunodiffusion was performed to determine antigen concentration (5 mg/ml). Lymphocyte suspensions were prepared on each patient and control and were incubated with 2 μCi of tritiated thimidine in the presence of tumor antigen or PHA. Blastogenic responses were calculated as dpm of tritiated thymidine incorporated. Tumor extracts were tested for potential cytotoxic effect and were found to be negative with both autologous and homologous lymphocytes, and with 10% homologous serum tumor extract was shown to have no inhibitory effect. It was found that four tumor extracts shared the major precipitin band of pooled tumor extracts indicating the presence of cystadeno carcinoma associated antigens in these extracts and only those extracts which had tumor associated

antigens were used in the tests. Lymphocytes of controls showed a blastogenic response to PHA which ranged from 76,694 to 965,160 dpm and those of cancer patients ranged from 26,301 to 737,588 dpm. On serial determinations no permanent depressions of response was seen in any patients' lympocytes. The mean ratio of tritiated thymidine incorporation into lymphocyte cultures containing tumor antigens compared to cultures without antigens was 1.33 in 10 of 11 cancer patients and 1.5 in 10 controls; these ratios are not significantly different. Addition of PHA and tumor antigen to the cultures showed no significant decrease in blastic response. It was concluded that there was no evidence shown of a cell mediated type of immune reactivity against autologous tumor extracts in ovarian cancer patients. This lack of response however, was not felt to be due to inability of lymphocytes to undergo blastogenesis since good response to PHA was found. It was also suggested that blastogenic transformation may be an inappropriate method for assaying the tumor antigens in question.

4487 TUMOUR ANTIGENICITY IN OVARIAN CANCER. (Eng.) Levin, L. (Medical Coll. St. Bartholomew's Hosp., London, England); McHardy, J. E.; Durling, O. M.; Hudson, C. N. *Br. J. Cancer* 32(2): 152-159; 1975.

Transformation of lymphocytes from patients with ovarian cancer after challenge with crude extracts of ovarian cancer cells was studied. The transformation into lymphoblasts, (blastogenic response) was studied using cells from 48 patients with ovarian cancer (9, autologous, 39 allogeneic), in 26 female controls matched for age and in 18 female patients with other types of cancer in remission from disease. The responses in ovarian cancer patients in remission and relapse were considered separately. The blastogenic responses to cell extracts of fetal ovary, fetal lung, fetal liver and normal adult ovary were also assessed in a proportion of all three groups. The blastogenic responses to ovarian cancer and fetal ovary cell extracts were found to be significantly greater in the ovarian cancer patients in remission than in the controls, but the responses to ovarian cancer extract were not greater in the relapse group or in patients with other cancers. As a blastogenic response to normal ovarian extract was also present in some of these patients, the data so far do not support the hypothesis of a tumor-specific antigen. This tumor-associated response may be occurring to determinants in fetal or adult ovarian tissue to which the patient becomes sensitized in malignant disease.

4488 SHARED IDIOTYPIC DETERMINANTS ON B AND T LYMPHOCYTES REACTIVE AGAINST THE SAME ANTIGENIC DETERMINANTS: II. DETERMINATION OF FREQUENCY AND CHARACTERISTICS OF IDIOTYPIC T AND B LYMPHOCYTES IN NORMAL RATS USING DIRECT VISUALIZATION. (Eng.) Binz, H. (Dept. Immunology, Uppsala Univ., Uppsala, Sweden); Wigzell, H. *J. Exp. Med.* 142(5): 1218-1230; 1975.

The frequency of normal idiotypic T and B lymphocytes reactive against an antigenic determinant(s) was determined using anti-idiotypic antibodies as a probe. Anti-idiotypic antibodies made against the antigen-binding receptors of T lymphocytes for a given antigen (*Ag-B* locus antigens in Lewis and DA rats) were shown to react with IgG antibodies of the same antigen-binding reactivity. Using such anti-idiotypic antibodies, normal Lewis T lymphocytes of B and T type could be visualized by the use of anti-(Lewis-anti-DA) antibodies. Visualization was possible using direct fluorescent antibody tests or autoradiography. Using the first technique and naked eye observations, 6.2% of normal Lewis T lymphocytes expressed idiotypic markers signifying anti-DA reactivity, whereas anti-DA-reactive B lymphocytes as measured by this approach was about 1.1%. Autoradiography on purified normal Lewis T lymphocytes gave similar figures. When comparing the intensity of fluorescence at the single cell level using quantitative cytofluorometry anti-idiotypic antibodies reactive with T lymphocytes gave a similar degree of intensity as was obtained using anti-Ig antibodies against B lymphocytes.

4489 SHARED IDIOTYPIC DETERMINANTS ON B AND T LYMPHOCYTES REACTIVE AGAINST THE SAME ANTIGENIC DETERMINANTS: IV. ISOLATION OF TWO GROUPS OF NATURALLY OCCURRING, IDIOTYPIC MOLECULES WITH SPECIFIC ANTIGEN-BINDING ACTIVITY IN THE SERUM AND URINE OF NORMAL RATS. (Eng.) Binz, H. (Uppsala Univ. Medical Sch., Box 562, 751 22 Uppsala, Sweden); Wigzell, H. *Scand. J. Immunol.* 4(5/6): 591-600; 1975.

To provide further information on the T cell antigen-binding receptor that shares idiotype with IgG antibodies against alloantigen, an investigation was carried out on the isolation and properties of naturally-occurring idiotypic molecules carrying the desired antigen-binding specificity. Rats used in the study were inbred Lewis, DN, and BN strains, possessing alloantigens $Ag\text{-}B^1$, $Ag\text{-}B^4$, and $Ag\text{-}B^3$, respectively, together with certain F_1 hybrids. T cells were prepared by fractionation of spleen or lymph node cell suspensions on columns of Degalan beads coated with rat Ig and rabbit anti-rat Ig. Anti-idiotypic antisera were prepared by immunizing (Lewis x DA)F_1 rats with Lewis T lymphocytes. Materials tested for presence of idiotypic molecules carrying the desired antigen-binding specificity were serum and urine, collected from normal Lewis rats. Assays for detection of anti-idiotypic molecules were based on inhibition of binding of known anti-idiotypic antisera to purified Lewis peripheral T cells in a previously developed procedure. For assays of antigen-binding capacity of the naturally occurring idiotypic factors to (L x DA)F_1 cells, the idiotypic preparations were first isolated from normal serum and urine by immunoabsorption onto anti-idiotypic immunoabsorbants, followed by labeling of the purified fractions with ^{125}I. It was found that sera and urine of normal rats contain naturally-occurring antibody-like molecules with reactivity to allogeneic Ag-B antigens. Such molecules contained both antigen-binding capacity for the relevant antigens and the idiotypic markers signifying such specific reactivity.

The preparations contained two groups of molecules, one around 7S in size and the other around 35,000 in molecular weight. Only the smaller molecules were found in the urine. Purified natural anti-Ag-B factors, when inoculated into rabbits or chickens, led to the production of anti-idiotypic antibodies that selectively inactivated rat T cells and that had the capacity to react against the relevant Ag-B antigens while leaving other reactivity intact. It is concluded that the system that was developed allows the purification of naturally-occurring idiotypic B- and T-cell products possessing antigen-binding specificity and is useful for further biochemical and functional analysis.

4490 ROLE OF B CELLS IN THE EXPRESSION OF THE PPD RESPONSE OF HUMAN LYMPHOCYTES *IN VITRO*. (Eng.) Blomgren, H. (Radiumhemmet, Karolinska Sjukhuset, S-104 01 Stockholm 60, Sweden). *Scand. J. Immunol.* 4(5/6):499-510; 1975.

An investigation was carried out to study the types of lymphocytes that are involved in the *in vitro* response to purified protein derivative (PPD) of tuberculin. A crude lymphocyte preparation, separated from blood of healthy human donors by centrifugation on a Ficoll-Isopaque gradient, was designated as nonpurified. Following removal of phagocytic cells by magnetic action on cells which had phagocytosed iron and by adherence to plastic Falcon flasks, T and B cells were separated from one another by incubation with SRBC, sedimentation of rosetted T cells in a Ficoll-Isopaque gradient, and collection of B cells from the fluid interphase. T cells were identified by their ability to form rosettes with SRBC; B cells were identified by their membrane-bound immunoglobulin molecules, using a fluorescent staining method. PPD stimulation of lymphocytes was assayed by a microculture technique involving uptake of ^{3}H-thymidine. The concentration of PPD used was 10 μg/ml. The results of kinetic studies on PPD stimulation of the different lymphocyte preparations showed that the nonpurified lymphocytes exhibited a peak thymidine uptake after seven days of culture, while the greatest proliferation of T cells occurred later, and B cells showed minimal isotope incorporation during the entire culture period. Although T and B cells cultured separately showed very weak responses during the first seven days of culture, mixtures of T and B cells were strongly stimulated during this period. Further, the response of the mixtures appeared optimal at a ratio of T cells to B cells of 1:1. Mitomycin treatment almost completely blocked the capacity the both T and B cells to incorporate thymidine when stimulated with PPD, and mixtures of mitomycin-treated T cells and normal cells yielded higher stimulation than mixtures of normal T cells or mitomycin-treated B cells. This indicated that T cells exposed to PPD release factors that stimulate B cells. Results of experiments on stimulatory effects of supernatant culture media from PPD-treated T or B cells confirmed the indication that PPD-stimulated T lymphocytes, but not B lymphocytes, released the stimulatory factors. The results did not show, however, whether PPD-stimulated lymphocytes release factors that are mitogenic for B-cells or merely potentiate their response t PPD. It appears that the expression of the *in vitro* PPD response of human lymphocytes is potentiated by the presence of B cells.

4491 SPONTANEOUS AKR LYMPHOMA WITH T AND B- CHARACTERISTICS. (Eng.) Greenberg, R. (Natl. Cancer Inst., Bethesda, Md. 20014); Zatz, M. *Nature* 257(5524)314-316: 1975.

Lymph nodes and spleens from AKR/J mice bearing t passaged AkTB-1 tumor line, derived from a sponta ous lymphoma in lymph nodes and spleen of a thyme tomized AKR/J mouse were examined for the presenc Thyl.1 antigen by an indirect specific-immunofluo cent staining technique. Spleen or lymph node ce were incubated with anti-Thyl.1 antiserum prepare hyperimmunization of CBA/J mice with AKT/J thymocytes. By day 12 of passage, more than 90% of ly node and spleen cells were Thyl.1-positive. Simi results were obtained with cells from AKR mice be ing a spontaneous thymoma or another passaged AKR lymphoma cell line derived from a spontaneous AKR thymoma. Late in passage almost all AkTB-1 spleen cells, but few lymph node cells, bore both IgM an Thyl.1 on their surfaces. Since the coexistence of T- and B-cell markers on the same cell is unus the possibility that either Thyl.1 or surface IgM was passively acquired was investigated. Late pas sage AkTB-1 spleen cells were capped by incubatio with unlabeled anti-Thyl.1 serum at 30 min at 4 C, followed by incubation with unlabeled anti-mouse γ heavy chain antibody for one hour at 37 C. Cells having IgM were similarly capped, but with a sing incubation with unlabeled anti-mouse Ig. As show by subsequent staining with fluorescein-conjugate anti-γ2, Thyl.1 and IgM caps formed immediately af ter incubation were neither shed nor redistribute over the cell surface following overnight incubati These results suggest that AkTB-1 spleen cells ca generate Thl.1 antigen and surface IgM. Late in p sage, when AkTB-1 spleen cells were 95% Thl.1 and 83% IgM-positive, they exhibited elevated spontane ous DNA synthesis that was depressed by phytohema glutinin (PHA) but markedly stimulated by lipopoly saccharide. These results further support the du nature of the spleen cells because LPS responsiven appears to be a characteristic of B cells, whereas PHA-induced inhibition of DNA synthesis is reporte a characteristic of some murine T-cell lymphoma li The progressive acquisition of B-cell characteris by AkTB-1 cells, as well as their differential expression in spleen and lymph nodes, suggest that t cells undergo differentiation *in vivo*; and that th lymphoid tissue microenvironment has a role in the control of this differentiation process.

4492 B- AND T-CELLS IN CANINE LYMPHOSARCOMA. (Eng.) Onions, D. E. (Sch. Veterinary Medicine, Univ. Cambridge, England). *Vet. Rec.* 97(6):108; 1975.

Characterization of lymphosarcomas into B and T cell forms by formation of complement-coated erythrocytes (EAC) and erythrocyte (E) rosettes was attempted. Cells from lymph node biopsies were

typed. Of 11 cases of multicentric lymphosarcoma, six contained 93-99% EAC rosetting cells and were classified as B-type. Three contained 42-79% and were classified as mixed. One case of thymic lymphosarcoma gave 13% EAC and 83% E rosettes and was considered T type. In the other cases, the percentages of rosetting cells was not close to 100, and these were not classified.

4493 STIMULATION OF SYNGENEIC AND ALLOGENEIC LYMPHOID CELLS BY TUMOUR CELLS *IN VITRO*. (Eng.) Potter, M. R. (Christie Hosp., Manchester M20 9BX, England); Balfour, B. M. *Br. J. Cancer* 32(5):5-15; 1975.

The *in vitro* response of syngeneic and allogeneic rat lymph node cells to tumor cells was investigated, as well as the lymph node cell response to phytohemagglutinin (PHA) stimulation and in mixed lymphocyte culture. 3,4-Benzpyrene in pellet form (10 mg) was implanted sc in young male Wistar and August rats; a second type of tumor was induced with 3-methylcholanthrene (5 mg) injected sc. August and Wistar rat lymph node cells responded well to PHA (0.04-4.0 μg/ml) stimulation and in mixed lymphocyte culture, as determined by an increased incorporation of ^{3}H-thymidine. August rat lymph node cells were also stimulated by incubation with irradiated (15,000 rad) syngeneic tumor cells. Allogeneic Wistar rat lymph node cells produced a larger response to the August tumor cells. The response of syngeneic and allogeneic lymph node cells was reduced by pretreating the tumor cells with a Wistar anti-tumor serum. Pretreating the tumor cells with sera from normal or tumor-bearing rats also reduced the response of syngeneic lymph node cells but did not reduce the response of allogeneic lymph node cells. These results are essentially the same as those previously reported for human and animal lymphocyte stimulation.

4494 ISOLATION AND PARTIAL CHEMICAL CHARACTERIZATION OF THF, A THYMUS HORMONE INVOLVED IN IMMUNE MATURATION OF LYMPHOID CELLS. (Eng.) Sook, A. I. (Dept. Cell Biology, Weizmann Inst. Science, Rehovot, Israel); Yakir, Y.; Trainin, N. *Cell. Immunol.* 19(1):151-157; 1975.

The isolation and characterization of a hormonal thymus factor (THF) are described. The hormone, which participates in processes leading to maturation and acquisition of immunocompetence in lymphoid cells, was obtained from calf thymus tissue by homogenization, ultracentrifugation, and dialysis. Assays for activity were based on an *in vitro* graft-*vs*-host reaction whereby THF enables parental mouse spleen cells to induce enlargement of spleen explants of newborn hybrid mice. The activity was found in the dialysate, and the THF was further purified by gel filtration on Sephadex G-10 and G-25 columns, followed by DEAE-Sephadex A-25 anion exchange chromatography. The THF eluted in the void volume on the Sephadex G-10 column and near the glucagon calibrating agent (molecular wt, 3,460) in the anion exchange column. The isoelectric point was 5.66-5.90, as determined by isoelectric focusing on polyacrylamide gels. The active principle showed positive Coomassie brilliant blue staining for protein but no Alcian blue staining for glycoprotein. The amino acid composition was found to be four residues of aspartic acid, one of threonine, five of serine, eight of glutamic acid, two of proline, five of glycine, two of alanine, one of leucine, one of lysine, and two of arginine. Based on leucine as a unit, the molecular wt was 3,220.

4495 IMMUNOCOMPETENT LYMPHOCYTES IN RATS HOSTING DMBA-INDUCED MAMMARY TUMOURS. (Eng.) Kellen, J. A. (Sunnybrook Medical Centre, 2075 Bayview Ave., Toronto, Ontario, M4N 3M5, Canada); Mirakian, A. *Wadley Med. Bull.* 5(1):1-7; 1975.

The binding of tumor-associated proteins of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors to peripheral lymphocytes and spleen cells of tumor-bearing animals was investigated. The binding was visualized by labeling the tumor proteins with fluorescein. The tumors were induced in female virgin Wistar rats. The tumors were removed by surgery, homogenized, and centrifuged at 150,000 x *g* for 60 min. The soluble protein of the supernatant was then labeled with fluorescein-isothiocyanate. Periperal lymphocytes were isolated from heparinized blood of tumor-bearing animals by centrifugation on Lymphoprep; spleen cells, by a similar procedure. The cells were incubated for 60 min at room temperature with the labeled tumor protein preparation, washed with saline, and prepared as a smear for UV microscopic observation. At least 1,000 cells were counted, and the incidence of fluorescence was assessed. The labeled proteins appeared to be bound to the membranes of the mononuclear cell preparations. All lymphocyte preparations from spleens of tumor-bearing hosts showed a frequency of fluorescent cells of 1-3%. This indicates that DMBA-induced mammary tumors contain specific soluble proteins that are antigenic and are recognized by the cellular immune system of the host. The percentage of fluorescent cells was lower in DMBA-injected rats without tumors, but not to a statistically significant degree. This suggests that even subclinical stages without apparent and palpable nodules already manifest themselves through the formation of specific tumor-associated proteins. No uptake of labeled tumor proteins was seen in lymphocytes of healthy controls. The results with preparations of lymphocytes from peripheral blood proved to be inconclusive.

4496 SPONTANEOUS ROSETTE AND ROSETTE-INHIBITION TESTS ON FRESH AND CRYOPRESERVED LYMPHOCYTES. (Eng.) Gross, R. L. (New England Deaconess Hosp., Boston, Mass.); Levin, A. G.; Peers, F. G.; Steel, C. M.; Tsu, T. *Cryobiology* 12(5):455-462; 1975.

Peripheral blood lymphocytes from 13 healthy adults (Africans, Asians, and Europeans, 24-53-yr-old) were compared in the fresh state and after controlled freezing in liquid nitogen. The mean percentage of cells forming spontaneous rosettes with sheep red blood cells was 52% in the fresh samples and 57% in frozen-thawed material. These figures are not

significantly different. Fresh and frozen cells proved equally sensitive to the action of an anti-lymphocyte globulin preparation in inhibiting rosette formation. It is clear that valid results may be obtained through the use of frozen preserved lymphocytes in rosette and rosette-inhibition tests.

4497 CLASSIFICATION OF LYMPHOCYTES IN NASOPHARYNGEAL CARCINOMA (NPC) BIOPSIES. (Eng.) Jondal, M. (Dept. Tumor Biology, Karolinska Inst., 10401 Stockholm 60, Sweden); Klein G. *Biomedicine* 23(5):163-165; 1975.

Seven biopsies taken from nasopharyngeal carcinoma (NPC) tissues were analyzed to establish the relative proportion of T and B cells. The vast majority of these cells had the capacity to form sheep RBC rosettes (mean 87%) and were thus classified as T cells. It is likely that the normal progenitor cell of NPC is susceptible to EBV infection. The regular genome-positive state of the anaplastic NPC-carcinoma cell suggests that this tumor preferentially, if not exclusively, arises from a genome carrying cell. Varying proportions of the infiltrating T-lymphocytes might represent a host cell sensitization against tumor-associated antigens.

4498 PHYTOHEMAGGLUTININ-INDUCED LYMPHOCYTE TRANSFORMATION IN NEWLY PRESENTING PATIENTS WITH PRIMARY CARCINOMA OF THE LUNG. (Eng.) Barnes, E. W. (Royal Infirmary, Edinburgh, Scotland); Farmer, A.; Penhale, W. J.; Irvine, W. J.; Roscoe, P.; Horne, N. W. *Cancer* 36(1):187-193; 1975.

The transformation of peripheral blood lymphocytes in response to phytohemagglutinin (PHA) was studied in 37 newly presenting patients who were subsequently proven to have carcinoma of the lung. When compared with healthy age- and sex-matched normal controls, no differences were noted in the thymidine uptake of the unstimulated lymphocytes in culture or in the response to any of the three dose levels of PHA used (0.32, 0.63, and 1.25 µl/ml). Neither the extent of the spread of the carcinoma nor the type of its histology showed any correlation with the PHA response, but the response was significantly depressed within 14 days of death in seven patients. The transformation indicies of normal lymphocytes in the presence of sera from 20 lung cancer patients at various stages in the disease and during treatment with BCG, compared with those obtained from sera of controls indicated no evidence for serum inhibitory factors in the lymphocytes of the cancer group. The results suggest that a primary depression in general lymphocyte responsiveness that could have accounted for the initiation of the disease does not occur. However, since depression does appear to follow the development of the disease, this suggests that the depression must be of a more selective nature, rather than a general loss.

4499 HETEROGENEITY OF T CELLS: DIFFERENT REPRESENTATIONS OF Ly ALLOANTIGENS ON KILLER CELLS AND HELPER CELLS. (Eng.) Oettgen, H. F. (Memorial Sloan-Kettering Cancer Center, New York, N.Y.); Kisielow, P.; Shiku, H.; Bean, M. A.; Hirst, J.; Hoffmann, M. K.; Boyse, E. A.; Old, L. J. *Transplant. Proc.* 7(1/Suppl. 1):473-475; 1975.

An attempt to distinguish subpopulations of T cells on the basis of their function is described. Mice (B6) were immunized with BALB/c spleen cells ip. Nonadherent peritoneal cells (NACP) from these mice were assayed for cytotoxicity against cells of a methylcholanthrene-induced BALB/c sarcoma. Ly-1.2 (C3H anti-CE thymocytes) and Ly-2.2 (anti-B6 leukemia ERLD) antisera lysed similar proportions of Thy-1-positive cells. Pretreatment with Ly-2.2 reduced the cytotoxicity of the remaining cell population by 63%, compared to 4% for Ly-1.2. The T-cell members of immune NACP populations must be heterogenous. Killer T cells in the peritoneal-cell population of the B6 mouse carry much Ly-2 antigen and little Ly-1 antigen. Functionally distinct subsets of T cells can be isolated on the basis of their surface characteristics.

4500 T-T INTERACTION IN THE GENERATION OF HELPE CELLS *IN VITRO*. (Eng.) Feldmann, M. (Dep Zool., Univ. Coll. London, England); Kilburn, D. G.; Levy, J. *Nature* 256(5520):741-743; 1975.

A study was conducted to determine whether or not th T helper cell response to antigen performic acid-oxi dized ferrodoxin (OFd) requires cooperation between two subpopulations of T cells. Cell populations wer primed *in vivo* to both (C hapten and N hapten) or to either of the individual determinants of OFd; these cells were then used *in vitro* to test for cell inter action during the development of helper cells to OFd Four series, each consisting of spleen cells of thre groups of mice, were primed (over a 1-yr period) wit either the N or C hapten conjugated to bovine serum albumins (N-BSA and C-BSA, respectively), or with OF Cells primed to N-BSA or C-BSA did not yield signifi cant numbers of helper cells. However, mixtures (1: of these cells produced responses yielding at least many helper cells as OFd-primed cells. Nylon wool-filtered spleen cells (<10% B cells) or anti-B and complement-treated spleen cells (<3% B) cooperated even more efficiently with B cells than helper cells (obtained from unpurified spleen); this indicates th the N- and C-primed cells were T cells. This was verified by experiments with anti-antisera. Inhibition of cooperative responses by unconjugated hapten was demonstrated; 10 µg/ml of N-BSV or C-BSA suppressed the response to 1 µ/ml OFd. The radioactive antigen-induced suicide technique was also used to verify the requirement for both N- and C-hapten-reac tive cells to generate helper cells to OFd; incubation of OFd-primed spleen cells or purified T cells with ^{125}I-labeled N- or C-BSA suppressed the helper response. Mixing the N- and C-suicided populations restored the OFd helper response to normal levels. On the basis of these three experimental procedures, it is concluded that N- and C-reactive T cells interact to generate helper cells to OFd.

4501 METALLIC COPPER-INDUCED GRANULOCYTE EXUDATION IN THE STUDY OF GRANULOCYTOPOIESIS. (Eng.) McGarry, M. P. (Dept. of Biological Resources, Roswell Park Memorial Inst., Buffalo, N.Y.). *Cell Tissue Kinet.* 8(4):355-360; 1975.

The use of metallic copper and glass rod implants to induce an acute, substantial granulocyte release and accumulation that would result in stimulated medullary granulocytopoiesis was investigated in female C3H/HeHa and C57Bl/6Ja mice. The rods (1.5 x 10 mm) were coated with melted paraffin at the tips and implanted into the peritoneal cavity. At various times following implantation, animals were anesthetized and bled aseptically to obtain serum for the assay of colony stimulating activity. Slides with peritoneal fluid and bone marrow smears were fixed for 50 min in methanol and stained with May-Grunewald-Giemsa for differential counting by oil immersion microscopy. Granulocytes were classified as eosinophil or neutrophil only if specific cytoplasmic granulation was obvious. Assay for the number of *in vitro* colony-forming cells was done using pairs of treated animals at six hours and 1, 2, 3, and 5 days after implantation. The implantation of either a copper or glass rod led to a significant accumulation of cells in the site of implant. The granulocyte response was most rapid, evident within six hours following implantation. In mice receiving rods of metallic copper, the response was significantly greater with respect to the total number of cells responding, as well as the percent involvement of granulocytes. There was an impressive stimulation of granulocytopoiesis, as evidenced by a substantial number of myeloblasts and promyelocytes on the second day and an overwhelming number of neutrophil myelocytes and metamyelocytes present by the fifth day. Stimulation was evident in marrow of glass rod-implanted mice but was not as extensive as that seen in the copper-rod-implanted mice. Serum levels of colony stimulating activity, an *in vitro* myeloproliferative stimulating activity, were elevated in copper rod-implanted mice for the entire study period as were femoral marrow agar-colony forming cells. Although the magnitude of the initial colony stimulating activity was greater in glass-rod implanted mice, there was no sustained elevation. It is concluded that metallic copper can be used effectively to induce a series of events resulting in stimulated granulocytopoiesis and that this reaction appears to be non-immunological in nature.

4502 COMPARISON BETWEEN MACROPHAGE ACTIVATION AND ENHANCEMENT OF NONSPECIFIC RESISTANCE TO TUMORS BY MYCOBACTERIAL IMMUNOADJUVANTS. (Eng.) Juy, D. (Centre National de la Recherche Scientifique and Institut Pasteur, 75015 Paris, France); Chedid, L. *Proc. Natl. Acad. Sci. USA* 72(10):4105-4109; 1975.

Experiments were performed with a view to determining whether a correlation exists between activation of macrophages by immunostimulants and the capacity of immunostimulants to enhance resistance to tumors *in vivo*. Macrophages were obtained from peritoneal exudates of (DBA2 x C57BL)-F1 mice. Peritoneal ascitic cells of mastocytoma P815, syngeneic for DBA2 mice, were used as target cells. In *in vitro* tests, monolayers of macrophages from normal mice were treated with various adjuvant and non-adjuvant preparations. In *in vivo* tests, macrophage monolayers were derived from mice treated ip with the different test preparations. Activation of the macrophages was determined by adding P 815 target cells to the monolayers, incubating for 24 hr, adding ^{3}H-thymidine four hours before the end of the incubation period, and measuring uptake of radioactivity in the cells. Results were expressed as percentage growth inhibition. The preparations tested for activity included pheno-killed *Mycobacterium smegmatis* cells; interphase material (IPM), a fraction extracted from *M. smegmatis;* Neo-WSA and WSA, two water-soluble adjuvants also extracted from *M. smegmatis;* muramyl dipeptide, a synthetic adjuvant component of the mycobacterial cell wall; muramyl L-alanine, a nonadjuvant cell wall component; and a lipopolysaccharide (LPS) prepared from *Salmonella enteritidis*. In the *in vitro* tests, WSA and the non-adjuvant muramyl peptide elicited weak responses, while IPM and the adjuvant muramyl peptide elicited strong responses. In the *in vivo* tests, macrophages from mice treated with IPM, New-WSA, WSA, or LPS strongly inhibited mastocytoma cell growth, while macrophages from mice treated with the muramyl peptides did not differ from those from normal mice. Macrophages of LPS- or WSA-treated mice were highly activated if they were harvested 4 or 8 days after *in vivo* stimulation, but this response decreased and disappeared later. In contrast, a very strong macrophage activation could still be demonstrated 64 days after injection of IPM. The antitumor effect of the IPM could not be related to a direct cytotoxic effect on the mastocytoma cells. Since of all the preparations tested, previous work had shown that only IPM protected mice against a syngeneic leukemia, it could be concluded that macrophage activation was correlated with adjuvant activity rather than with *in vivo* tumor activity.

4503 TOLERANCE INDUCTION WITH BOVINE γ GLOBULIN IN MOUSE RADIATION CHIMAERAS DEPENDS ON MACROPHAGES. (Eng.) Lukic, M. L. (Immunology Res. Center, Univ. Belgrade, Vojvode Stepe 458, 11000 Belgrade, Yugoslavia); Leskowitz, S. *Nature* 252(5484):605-607; 1974.

Carrageenin, a polysaccharide isolated from seaweed and known to be toxic for macrophages, was tested for its effects on tolerance induced in BALB/c mice by ultracentrifuged bovine γ globulin (sBGG, 2 mg, ip). sBGG was administered 24 hr after the last injection of carrageenin; one week later the mice with immunized with 100 μg-BGG in complete Freund's adjuvant (CFA) and then challenged with 2 μg ^{125}I-BGG. Pretreatment with 0.5 mg or 4 x 10.5 mg favored tolerance induction in the mice, whereas the immune response of mice pretreated with BGG-CFA only was not affected. In spleen cell transfer experiments, lethally irradiated (850 rads) DBA/2 mice were tested for tolerance induction after reconstitution with BALB/c bone marrow cells (2 x 10^{7}). The mice were injected with 2 mg sBGG 4, 6, or 12 wk after reconstitution, followed by immunization with BGG-CFA and then challenge with ^{125}I-BGG. At 4 and 6 wk after reconstitution, the mice showed nonimmune clearance typical or normal DBA/2 mice made tolerant. After 12 wk, 10 of 11 mice showed

the characteristic resistance to tolerance of the BALB/c donors. These results provide strong evidence that strain differences in the induction of tolerance by antigens such as BGG are related to an event occurring at the macrophage level.

4504 IMMUNOLOGICAL SIGNIFICANCE OF CERTAIN MORPHOLOGICAL ASPECTS OF SATELLITE LYMPH NODES OF LARYNGEAL CARCINOMAS. (Ita.) Cortesina, G. (Clinica Otorinolaringologica dell'Universita, 10100 Torino - Via Genova, 3, Italy); Pia, F.; Mancini, P.; Boido, C.; Giordano, C. *Cancro* 27(6): 373-388; 1974.

The behavior of lymphocytes and macrophages in tumor metastases of larynx carcinomas were studied in 14 men and 1 woman. A relatively low number of germinal centers were found in the early stages of disease, with an increase of these in the advanced stages. A strong hyperplasia of macrophages and T lymphocytes in cortical and paracortical sinuses was also observed in the early phases of tumoral diffusion. The results seem in accord with the response of body defense to tumoral invasion.

4505 OUABAIN BINDING TO INTACT LYMPHOCYTES: ENHANCEMENT BY PHYTOHEMAGGLUTININ AND LEUCOAGGLUTININ. (Eng.) Quastel, M. R. (Isotope Dept., Soroka Medical Center, Beer Sheva, Israel); Kaplan, J. G. *Exp. Cell Res.* 94(2):351-362; 1975.

A study was made of the kinetics of binding of ouabain as an indicator of membrane changes associated with lymphocyte blastoid activation by phytohemagglutinin (PHA), leucoagglutinin (LA), concanavalin A (Con A), and pokeweed mitogen (PWM). Cultures of lymphocytes derived from human peripheral blood were used throughout. ^{3}H-ouabain, dissolved in benzene-alcohol, was added to the cultures to give final concentrations varying from 10^{-8} to 10^{-6} M. The cell cultures were incubated at 37 C in the presence of the ^{3}H-ouabain for 1-33 hr; at different times, cells were removed and tested for radioactivity. The results were expressed in terms of the number of ouabain glycoside molecules taken up by the cell. Both PHA and LA increased the rate of binding of the glycoside within minutes. The saturation number of binding sites was estimated to be 1.25 x 10^5/cell for nonstimulated lymphocytes. PHA caused the saturation level to rise to values of about 2.3 x 10^5/cell. The rate of ^{3}H-ouabain binding was very sensitive to potassium concentration, and the specificity of ^{3}H-ouabain binding to K^+ receptors on the lymphocytes was demonstrated by the inhibitory effect of K^+ at various concentrations on the degree of binding. The very early increase in both ouabain binding and ^{42}K transport for mitogen-stimulated cells, the increase in V_{max} though not K_m found for both ^{3}H-ouabain and ^{42}K transport, and the similar increase of ^{3}H-ouabain binding compared with that of ^{42}K transport following PHA administration all support the view that ^{3}H-ouabain serves as a label for the K^+ site. Both ouabain and digoxin displaced the label. Estimates were provided for the affinity constants for uptake and turnover of ouabain on the lymphocyte surface. Preliminary studies with Con A and PWM did not reveal an equivalent stimulation of ^{3}H-ouabain binding. These agents are known, however, to differ from PHA in their specificity for lymphocyte subpopulations, in their agglutinating effects, and in the dynami characterizing their induction of transformation.

4506 LECTIN AGGLUTINABILITY OF NON-NEOPLASTI AND NEOPLASTIC HUMAN LYMPHOID CELLS *IN VITRO*. (Eng.) Glimelius, B. (The Wallenberg Lab Univ. of Uppsala, Uppsala, Sweden); Nilsson, K.; Ponten, J. *Int. J. Cancer* 15(6):888-896; 1975.

To resolve the question of whether lectin aggluti ability is related to neoplasia *per se* or to the prevailing functional state, a study was carried out on the agglutinability of benign and malignan lymphoid cells in different objectively verifiabl functional states. The types of cells which were tested included normal and phytohemagglutinin (PH stimulated human peripheral lymphocytes and 21 established lines of hematopoietic origin. These cell lines were classified as non-neoplastic (lymphoblastoid) or neoplastic (lymphoma, leukemia, myeloma, etc.). The lines were maintained as stationary cultures. When agglutination tests were performed with concanavalin A (Con A), a concentration of 100 µg/ml was used and the degree of agglutination was expressed as the percentage of cells trapped in agglutinates. When *Ricinus communis* agglutinin (RCA) was used, the degree of agglutinability was based on the concentration of RCA required to cause 50% agglutination. It was found that no systematic correlation existed between the neoplastic state and sensitivity to Con A or RCA. In general, cells of neoplastic lines varied unsystematically in their surface propertie as evaluated by Con A agglutination. The possible exception was noted that the presence of Epstein-Barr virus (EBV) was associated with a high degree of agglutination. Further, cells of diploid lymphoblastoid lines and PHA-stimulated lymphocytes agglutinated similarly and significantly better than unstimulated T- or B-lymphocytes. It was pro posed that the relatively simple Con A agglutination assay can be used as an adjunct in classification of human lymphoid cell lines. A finding th EBV-carrying established lymphoblastoid cells and PHA-stimulated lymphocytes exhibited the same degree of lectin agglutinability suggested that acti vation of resting lymphocytes rather than capacity for endless proliferation is responsible for the altered response to Con A or RCA.

4507 DIFFERENCES IN DENSITY OF CONCANAVALIN A-BINDING SITES DUE TO DIFFERENCES IN SURFACE MORPHOLOGY OF SUSPENDED NORMAL AND TRANSFORMED 3T3 FIBROBLASTS. (Eng.) Collard, J. G. (Netherlands Cancer Inst., Sarphatistraat 108, Amsterdam, Netherlands); Temmink, J. H. M. *J. Cell Sci.* 19(1):21-32; 1975.

Calculations of the density of concanavalin A (Con A)-binding sites on normal and transformed fibroblasts have, as yet, been based on the un-

proven assumption that suspended cells are smooth spheres. The surface morphology of suspended normal and simian virus 40-transformed fibroblasts were studied with scanning and transmission electron microscopes. A large difference was found in surface morphology between suspended normal and transformed 3T3 cells. When this difference in surface morphology was taken into account, the estimated cell surface area of normal cells was approximately seven times larger than that of transformed cells, the density of Con A-binding sites is approximately seven times greater on transformed than on normal 3T3 cells. The difference in density of Con A-binding sites between normal and transformed fibroblasts might be sufficient to explain the difference in agglutination response, and may also be the cause of the different degrees of clustering of Con A-binding sites on the plasma membrane of these cells.

4508 IMMUNOLOGIC ENHANCEMENT OF LEUKEMIA L1210 BY *CORYNEBACTERIUM PARVUM* [abstract]. (Eng.) Berd, D. (Yale Univ., New Haven, Conn. 06510); Mitchell, M. S.; Marsh, J. C. *Proc. Am. Assoc. Cancer Res.* 16:6; 1975.

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4536 AUGMENTATION OF LYMPHOCYTE CYTOTOXICITY BY ANTIBODY TO *HERPESVIRUS SAIMIRI* ANTIGEN [abstract]. (Eng.) Prevost, J.-M. (Natl. Inst. Health, Bethesda, Md.); Pearson, G. R. *Proc. Am. Assoc. Cancer Res.* 16:64; 1975.

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Tsang, K. Y.; Blakemore, W. S. *Proc. Am. Assoc. Cancer Res.* 16:119; 1975.

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4551 IMMUNOLOGICAL STUDIES ON HUMAN CHRONIC MYELOGENOUS LEUKEMIA CELLS [abstract]. (Eng.) Whitson, M. E. (Univ. Tennessee). *Diss. Abstr. Int. B* 35(11):5504-5505; 1975.

4552 MEASUREMENT OF SPECIFIC IMMUNE RESPONSES IN ACUTE LYMPHOCYTIC LEUKAEMIA OF CHILDHOOD. (Eng.) O'Keefe, D. E. (Royal Children's Hosp. Res. Found., Melbourne, Australia); Wilson, F. C.; Ekert, H.; Jose, D. G. *Clin. Exp. Pharmacol. Physiol.* 2(1):80-81; 1975.

4553 THE APPLICATION OF ROSETTE-FORMATION TEST IN THE EVALUATION OF IMMUNOLOGICAL REACTIVITY IN PATIENTS WITH MELANOMA. (Rus.) Trapeznikov, N. N. (Inst. Exp. Clin. Oncol., Acad. Med. Sci. U.S.S.R., Moscow, U.S.S.R.); Kupin, V. I.; Radzikhovskaia, R. M.; Kadagidze, Z. G. *Dokl. Akad. Nauk S.S.S.R.* 222(2):468-471; 1975.

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4555 IMMUNOLOGIC INDUCTION OF RETICULUM CELL SARCOMA: DONOR-TYPE LYMPHOMAS IN THE GRAFT-VERSUS-HOST MODEL. (Eng.) Gleichmann, E. (Medizinische Hochschule Hannover, D-3000 Hannover, Karl-Wiechert-Allee 9, West Germany); Peters, K.; Lattmann, E.; Gleichmann, H. *Eur. J. Immunol.* 5(6):406-412; 1975.

See also:

* (Rev): 4214, 4215, 4216, 4218, 4237, 4240, 4246, 4247, 4248, 4249, 4250, 4251, 4252, 4253, 4261, 4263
* (Chem): 4293
* (Viral): 4403, 4404, 4424, 4434
* (Path): 4557, 4566, 4582, 4587, 4594, 4601
* (Epid-Biom): 4650

4556 MULTIPLE NEOPLASMS IN TWO SIBLINGS WITH A VARIANT FORM OF FANCONI'S ANEMIA. (Eng.) Sarna, G. (S. Perry, Natl. Inst. Health, Building 1, Room 111, Bethesda, Md. 20014); Tomasulo, P.; Lotz, M. J.; Bubinak, J. F.; Shulman, N. R. *Cancer* 36(3):1029-1033; 1975.

The case reports of two brothers with a variant form of Fanconi's anemia who developed multiple neoplasms after prolonged survival and treatment with androgens are described. The patients were diagnosed at ages 7 and 10 yr as being Fanconi's anemia variants on the basis of marrow hypoplasia, family history, multiple chromosomal aberrations, and, in one who was tested, abnormal fibroblast transformation with Simian virus 40. The first brother received total cumulative doses of testosterone cyclopentyl proprionate (16.8 g), norethandrolone (31.6 g), oxandrolone (2.2 g), and oxymethalone (9.0 g) over 75 mo. The second brother received norethandrolone (56.7 g), oxandrolone (2.1 g), and oxymethalone (1.2 g) over 88 mo. The first brother developed two separate oral squamous cell carcinomata, and the other developed acute leukemia and hepatoma. Androgens may have had a carcinogenic role in the appearance of the hepatic neoplasm. There is an increased incidence of neoplasm associated with Fanconi's anemia. This may be related to frequent spontaneous chromosomal aberrations and/or to increased cellular susceptibility to viral transformation.

4557 CUTANEOUS T-CELL LYMPHOMAS: THE SEZARY SYNDROME, MYCOSIS FUNGOIDES, AND RELATED DISORDERS. (Eng.) Lutzner, M. (Natl. Cancer Inst., Bldg. 10, Room 12N-238, Bethesda, Md. 20014); Edelson, R.; Schein, P.; Green, I.; Kirkpatrick, C.; Ahmed, A. *Ann. Intern. Med.* 83(4):534-552; 1975.

Neoplastic T cells from four patients with the Sezary syndrome were unable to translate various membrane stimuli, which included responses to phytohemagglutinin, concanavalin A, mitomycin C, allogeneic cells, blastogenic factor, and the mitogenic activity of anti-T-cell serums. This lack of reactivity was not secondary to the production of inhibitors. Cells from these patients also lacked the ability to kill antibody-coated target cells. Cells from these patients did not produce migratory inhibitory factor in response to various stimuli; plasma from these patients did show migratory-inhibitory-factory-like activity. The Sezary cells seem to be T cells with abnormalities intrinsic to their neoplastic nature. It seems appropriate to classify the large and small cell variants of the Sezary syndrome, mycosis fungoides, and related lymphoproliferative disorders under the broad heading "cutaneous T-cell lymphomas." In all cases, the processes seem to originate in the skin, and quite remarkably the thymus remains uninvolved.

4558 ON A MALIGNANT VARIANT OF ABRIKOSOV'S TUMOURS. (Rus.) Apatenko, A. K. (No affiliation); Sementsov, P. N. *Arkh. Patol.* 37(2): 16-21; 1975.

A malignant variant of Abrikosoff's tumor was found in two men and one woman. The tumor was localized in the soft tissues of a finger, under the skin of the upper lip and in the soft tissues of the lumba region, respectively. Locally destructive infiltrative growth, polymorphism of the cells and nucl irregular patterns of amitotic cell division, and hyperchromatism of the cell nuclei were the charac teristic features of all tumors. Isolated polynuclear cells were also found.

4559 GIANT MELANOSOMES IN MOLES AND IN NORMAL HUMAN EPIDERMIS. (Ger.) Konrad, K. (Abteilung fur Experimentelle Dermatologie, I. Universitats-Hautklinik, Vienna, Austria); Honigsmann, H. *Wien. Klin. Wochenschr.* 87(5):173-177; 1975.

Giant melanosomes were found in normal human epidermis (two cases), in nevi (four cases), and in melanoderma (one case). This finding indicates that giant melanosomes are not diagnostic for von Recklinghausen's disease (neurofibromatosis).

4560 NEVUS SPILUS--A PIGMENT NEVUS WITH GIANT MELANOSOMES. CLINICAL, HISTOLOGICAL AND FINE STRUCTURAL ASPECTS. (Ger.) Konrad, K. (I. Univ-Hautklinik, Alserstrasse 4, A-1090 Wien, Austria); Honigsmann, H.; Wolff, K. *Hautarzt* 25 (12):585-593; 1975.

Clinical, histological and fine structural aspects of nevus spilus in ten patients (six men and four women, aged 18-65 yr) are described. Nevus spilus had been present since childhood in six patients, but it was impossible to determine whether it was inborn. Neither the anamneses nor the clinical examinations furnished any indication of Recklinghausen's disease or other systemic diseases involving pigmentation disturbances. Despite the presence of nevus cells, the chance of malignant tran formation is slim. The giant melanosomes detected in part of the melanocytes and in nevus cells are interpreted as an expression of disturbances in the morphogenesis of individual melanosomes rather than as disturbances in melanogenesis or in pigment formation. The giant melanosomes contain active tryosinase. It was possible to distinguish these melanosomes from granules found in Chediak-Higashi syndrome. Giant melanosomes are assumed to occur also in pigment disturbances other than nevus spilu

4561 SUBCUTANEOUS ANGIOLYMPHOID HYPERPLASIA (KIMURA DISEASE). REPORT OF A CASE. (En Kim, B. H. (Lutheran Medical Center, Brooklyn, N.Y. 11220); Sithian, N.; Cucolo*, G. F. *Arch. Surg.* 110(10):1246-1248, 1975.

A case of subcutaneous angiolymphoid hyperplasia (Kimura disease) examined at its early stage is reported. A ten-year-old boy presented with a nontender, movable, and firm mass growing in his left cheek. Results of laboratory tests were withi normal limits, and no blood eosinophilia was reported. Under general anesthesia, a transverse incision was made over the buccal aspect of the

cheek, the buccinator muscles were bluntly separated, and the mass was identified in the subcutaneous tissue and completely excised. Microscopic examination of the grayish-tan specimen showed a well-circumscribed lesion surrounded by thin layers of fibrous connective tissue. The main pathologic findings were exuberant proliferation of small blood vessels lined with plump endothelial cells, and infiltration by moderate numbers of lymphocytes in the stroma. Small numbers of scattered eosinophils and histiocytes were also noted. A brief literature review notes the predominant occurrence of the lesion in the subcutaneous tissue; preferential use of the inclusive term "angiolymphoid hyperplasia" is suggested.

562 ENDOCARDIAL PAPILLARY ELASTOFIBROMAS. HISTOLOGIC, HISTOCHEMICAL, AND ELECTRON MICROSCOPICAL FINDINGS. (Eng.) Fishbein, M. C. (Natl. Heart Lung Inst., Natl. Inst. Health, Bethesda, Md.); Ferrans, V. J.; Roberts, W. C. *Arch. Pathol.* 99(6):335-341; 1975.

Three cases of solitary endocardial papillary elastofibromas found at necropsy were studied histologically. The organization of cellular and extracellular components appeared similar and as distinctive in the three cases. Each tumor papilla contained (a) a dense, central core of collagen and elastic tissue (b) a peripheral, myxomatous layer with deposits of acid mucopolysaccharides, and (c) an overlying, hyperplastic layer of endothelial cells. Ultrastructural study of one tumor showed that the cells in all three tumors had numerous cytoplasmic filaments, 100 A in diameter, and dilated cisterns of endoplasmic reticulum; endothelial cells also had intercellular junctions and numerous pinocytotic vesicles. The myxomatous stroma varied from amorphous to fibrillar, and the collagenous cores showed focal degeneration. The name "endocardial papillary elastofibroma" is suggested to emphasize those features that are most conspicuous and serve to differentiate this tumor from myxoma.

563 FIBROUS HISTIOCYTOMA OF THE CORNEOSCLERAL LIMBUS. (Eng.) Faludi, J. E. (Johns Hopkins Hosp., 601 N. Broadway, Baltimore, Md. 21205); Kenyon, K.; Green*, W. R. *Am. J. Ophthalmol.* 80(4):619-624; 1975.

Clinical, histopathological, and ultrastructural findings of a case of fibrous histiocytoma that developed at the corneoscleral limbus are presented. A 21-yr-old Caucasian woman presented a progressively enlarging mass lesion at the inferotemporal corneoscleral limbus of the left eye. After ineffective initial therapy of 1/8% prednisolone ophthalmic drops, incomplete excisional biopsy and subsequent complete excision by lamellar keratectomy and sclerectomy were performed. The entire specimen was prepared for routine histopathologic and histochemical study. By light microscopy, the tumor appeared diffusely cellular, localized, unencapsulated, and confined to the subepithelial connective tissue of the corneoscleral limbus and peripheral cornea. Electron microscopy revealed large histiocytic epithelioid cells characterized by lobulated nuclei with marginal chromatin, irregularly ruffled plasma membranes with interdigitating processes, and numerous small intracytoplasmic vacuoles with pleomorphic contents. The fibrocytic cells were fusiform in configuration with ellipsoid nuclei and extended cytoplasmic processes. The cell membrane was often closely associated with the randomly arrayed collagenous fibers of uniform diameter. The lack of systemic disease and clinical behavior of the enlarging tumor suggested a benign fibrous histiocytoma.

4564 THE NATURAL HISTORY OF MALIGNANT MELANOMA OF THE CHOROID: SMALL VS LARGE TUMORS. (Eng.) Davidorf, F. H. (Dep. Ophthalmol., Ohio State Univ., Columbus); Lang, J. R. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 79(2):310-320; 1975.

The growth characteristics and natural history of 264 malignant melanomas of the choroid were studied. Small melanomas were compared with larger melanomas. Of the 264 melanomas, 50 were designated as small melanomas (less than 10 mm in diameter and 3 mm in elevation). A large percentage (22.0%) of mixed and epithelioid tumors (considered to be more malignant) were found in the group of small tumors. In 33 patients with a possible five-year survival, two (6.1%) died of metastases. Of 22 possible ten-year follow-ups, five patients died of metastatic melanoma (22.7%). These deaths occurred in one patient with a spindle cell A melanoma, three with spindle cell B melanomas, and one with a mixed melanoma. All five of these patients were women, and all had posterior pole tumors. No deaths occurred in patients with tumors less than 7 mm in diameter and 2 mm in elevation. The relatively good five-year survival in the patients with smaller melanomas supports the views held by previous authors that small melanomas carry a better prognosis than larger tumors. However, mixed and epithelioid tumors in this series do not seem to have a worse prognosis than spindle cell tumors. Cell type may be of less prognostic significance that tumor size in the case of small melanomas.

4565 GASTRIC MUCOSAL DYSPLASIAS: WHAT IS THEIR CLINICAL SIGNIFICANCE? (Ger.) Oehlert, W. (Pathologisches Institut der Universitat, 78 Freiburg, Albertstr. 19 West Germany); Keller, P.; Henke, M.; Strauch, M. *Deutsch. Med. Wochenschr.* 100(39):1950-1956; 1975.

Using criteria of proliferation kinetics, karyometry, histology and histochemistry, definition of normal and dysplastic surface epithelium of the gastric mucosa was attempted. Instead of such terms as surface carcinoma, intra-epithelial carcinoma and carcinoma-in-situ, the term dysplasia III of the surface epithelium is suggested. Serial biopsies (2-5) during 1 mo to 2 yr, of gastric mucosa from 285 patients with dysplasia II/III, demonstrated reversibility or persistence of such changes without transition into early carcinoma. In this series, 116 (40.7%) of the lesions im-

proved, 142 (49.8%) were unchanged, and 27 (9.5%) progressed. Of the 8,262 (3,539 women) patients biopsied in this 2 yr study, 5,639 had pathologic findings.

4566 PRIMARY BILIARY CIRRHOSIS WITH CANCER OF THE AMPULLA OF VATER. (Eng.) Makipour, H. (Cleveland Clinic, Cleveland, Ohio); Winkelman, E. I. *Cleve. Clin. Q.* 42(2):209-213; 1975.

A case history is presented of carcinoma of the ampulla of Vater occurring with primary biliary cirrhosis and the value of the antimitochondrial antibody and the potential role of endoscopic retograde cholangiopancreatography in establishing a correct diagnosis is discussed. A 57-yr-old woman presented with jaundice and diarrhea of 8-9 mo duration. Other complaints were mild right upper quadrant abdominal discomfort, generalized bone pain, and a 3.6-kg wt loss. Antimitochondrial antibody was positive at greater than 1:600 serum dilution; smooth muscle antibody and antinuclear factor were negative. Other clinical findings were interpreted as compatible with primary biliary cirrhosis. She was discharged and a high protein diet and diphenoxylate hydrochloride were prescribed for control of the diarrhea. During the next six months pruritus appeared and the diarrhea and weight loss continued. The patient was readmitted to the hospital; the results of physical examination were unchanged, except for the presence of bilateral periobital xanthelasma. At laparotomy a 3.5-cm firm, rubbery mass was found in the head of the pancreas. Operative cholangiogram showed complete obstruction of the distal common duct with proximal dilatation. Transduodenal biopsy of the ampulla of Vater showed well-differentiated adenocarcinoma. The patient tolerated a Whipple's procedure well but for the next 30 mo continued to have severe diarrhea and generalized bone pain. The patient died on the fourth day after being readmitted to the hospital. Autopsy showed the capsular surface of the liver was finely nodular and the entire liver parenchyma was deep green. There was no evidence of recurrence of metastatic tumor. A review of the literature indicated that the antimitochondrial antibody is an accurate, sensitive test that is positive in 80-85% of all patients with primary biliary cirrhosis and falsely positive in only 2-4%. Lesions of the biliary tract, however, can produce a false positive test result, and these lesions can coexist with primary biliary cirrhosis. Since the iv cholangiogram does not visualize the biliary tree in most cases, diagnostic studies are limited to the transhepatic cholangiogram or endoscopic retrograde cholangiopancreatography. Some physicians are reluctant to use percutaneous transhepatic cholangiography as a routine procedure because of reported complications. Endoscopic retrograde cholangiopancreatography has been used successfully to exclude obstruction in the biliary tree and is probably the safest procedure at present.

4567 RUPTURED BENIGN HEPATOMA ASSOCIATED WITH AN ORAL CONTRACEPTIVE: A CASE REPORT. (Eng.) Stenwig, A. E. (Norwegian Radium Hosp., Montebello, Oslo 3, Norway); Solgaard, T. *Virch Arch.* [*Pathol. Anat.*] 367(4):337-343; 1975.

A ruptured benign hepatoma in a woman at full-ter pregnancy is described. Some peliosis hepatis wa found. The patient (31 yr-old) had used an oral contraceptive for eight yr before pregnancy. Twe three similar cases have been found in the literature; 14 were not diagnosed before rupture. The present tumor differed from previously described lesions by containing foci of hematopoietic cells As there were no signs of blood or bone marrow disease, it is suggested that the extramedullary hematopoiesis is a constituent of the tumor tissu This lesion should be considered in any case of a woman on oral contraceptives presenting with upper abdominal symptoms.

4568 ADENOMATOID ODONTOGENIC TUMOR (ADENOAME BLASTOMA): REPORT OF A CASE. (Eng.) Milobsky, L. (1800 Eye St., N.W., Washington, D.C 20006); Milobsky*, S. A.; Miller, G. M. *Oral Sur* 40(5):681-685; 1975.

A case of adenomatoid odontogenic tumor in which trauma was apparently a significant causal factor is presented. Beginning at age 11 yr, the patien (male) underwent two surgical procedures to expos the crown of the mandibular left cuspid. During the second procedure, a pin was cemented into the crown and orthodontic traction was applied to bri the tooth into position. A lingual retainer was subsequently cemented to the mandibular cuspids with orthodontic bands, one of which caused long-term chronic irritation. X-ray examination appro mately 2.5 yr after the second surgical procedure revealed a large radiolucent area surrounding the mandibular left cuspid. The gingival papillae were grossly distorted, and a hard, dense swellin filled the mucobuccal fold. Removal of a small portion of the thin and distended cortical plate disclosed a solid tumor mass. Consultation with an oral pathologist resulted in the diagnosis of adenoameloblastoma and prevented unnecessary radic surgery. The tumor was thoroughly curetted, and there is no evidence of recurrence after 18 mo. The two surgical procedures could have easily "seeded" cellular elements of the developmental cyst into adjacent tissues; the severe chronic irritation inflicted on these tissues by the ortho dontic appliance was probably sufficient to stimulate neoplastic changes in the seeded tooth germ epithelium.

4569 MULTIPLE AND MULTIFOCAL CARCINOMAS IN FEMALE GENITAL ORGANS AND BREAST. (Eng. Deligdisch, L. (Ichilov Municipal Hosp., 6, Weizma St., Tel-Aviv, Israel); Szulman, A. E. *Gynecol. Oncol.* 3(3):181-190; 1975.

Sixty-seven cases of multiple primary malignant tumors of the female genital organs and breast wer analyzed, and 13 cases of multifocal primary tumor in similar organs were also examined. The 67 case represented 5.4% of the total cancer cases (1235) seen in a single hospital over a 5-yr period. The

combinations of the different multiple primary tumors were as follows: female genital organs or breast and extragenital (23); breast and genital organs (17); cervix and vulva or vagina (13); endometrium and ovary (10); cervix and endometrium (5); and ovary and cervix (2). In seven cases, an association of more than two primary malignant tumors was found. The involved organs were breast, ovary, endometrium, cervix, vagina, urinary bladder, and appendix in various combinations and time sequences. Endometriosis of ovaries and myometrium was found in 14 patients, nine of which had ovarian and endometrial carcinoma. A history of radium therapy was found in five cases, all of them with metachronously appearing tumors (1, 8, and 18 yr after therapy). A higher incidence of multiple primary cancers was found in embryologically related organs (i.e. vulva, vagina, and uterine exocervix, or endometrium and ovary). Endometriosis with malignant foci was frequently found associated with the multiple primary tumors of the mullerian epithelium of various locations. Carinoma *in situ* was found synchronously with overt multiple and multifocal carcinoma of the genital organs and breasts and was therefore considered as a previous stage of the carcinomatous progression. No conclusions could be drawn about the eventual pathogenic relationship between mammary dysplasia and carcinoma of the breast, since mammary dysplasia was found both synchronously and metachronously with overt and *in situ* carcinomas of the breasts. It is suggested that multiple primary tumor development probably requires not only a common embryologic origin but also a carcinogenic influence that is operative nearly equally throughout, such as hormones or radiation.

570 URINARY EXRETION OF STEROIDS BY JAPANESE WOMEN WITH BREAST CANCER. (Eng.) Tomingga, T. (Dept. Oncologic Surgery, Res. Inst. for Microbial Diseases, Yamada-kami, Suita, Osaku-fu 565 Japan); Tei, N.; Kitamura, M.; Taguchi, T.; Sudo, Y.; Sato, S. *Gann* 66(3):305-310; 1975.

The urinary excretion of steroids was studied in 25 premenopausal Japanese patients with advanced breast cancer in the nonmenstrual phase and in 20 healthy controls in the follicular phase, ovulatory stage, and luteal phase. Twenty-four hour urine samples were assayed for estrogens by radioimmunoassay, for 17-hydroxycorticosteroid by the Porter-Silber reaction, and for total 17-ketosteroids. The urinary 17-ketosteroids were fractionated on silica gel columns and analyzed by gas-liquid chromatography. Among the controls, the urinary total estrogen levels were highest in the ovulatory stage (80.6 μg/day) and lowest in the follicular phase (37.9 μg/day). The total estrogens in the cancer patients was 26.5 μg/day. The urinary estrone values were lower in the cancer patients (4.5 μg/day) than in the controls (7.9-21.2 μg/day), as were the estriol values. The estradiol levels were similar in the cancer patients and controls in the follicular and luteal phases, but were higher in the ovulatory stage controls than in the cancer patients. Similarly, the 17-hydroxycorticosteroid levels in the luteal phase and ovulatory stage controls were lower than those in the cancer patients, but were similar in the cancer patients and follicular phase controls. The urinary 17-ketosteroid levels were lower in the cancer patients than in the controls. However, among the 17-ketosteroid fractions, the level of dehydroepiandrosterone was higher in the cancer patients than in the ovulatory controls; the levels of etiocholanolone and androsterone were similar in the two groups.

4571 CANCER OF THE VAGINA. (Eng.) Davis, P. C. (Doctors' Building, NW Annex, Asheville, N. C. 28801); Franklin, E. W., III. *South. Med. J.* 68(10):1239-1242; 1975.

Experience in the diagnosis and management of 37 cases of cancer of the vagina is reported. Twenty-five of the 37 patients had squamous cell carcinoma of the vagina, and seven of these cases were intraepithelial. The remaining 12 patients had sarcoma, melanoma, or adenocarcinoma. All but four of the patients with squamous cell carcinoma were over 50 yr old; among the patients with sarcomas of diverse histologic types, the age range was 2.5-77 yr. Bleeding or bloody vaginal discharge was the most common presenting symptom with all cell types. Exophytic lesions accounted for 46% of the 30 invasive cancers, including 50% of the epidermoid carcinomas. In 60% of the cases, the lesion was located in the upper portion of the vagina. Seven of the 37 patients had a second primary malignancy, including two lesions of the skin beyond the anogenital epithelium. One patient had a stage I adenocarcinoma of the endometrium and another had a large squamous cell carcinoma of the lung. Three patients had previously been treated for carcinoma *in situ* of the cervix by hysterectomy. Over half the patients received radiation therapy, usually external cobalt radiation. Primary surgical treatment in one-third of the patients ranged from local resection or vaginectomy with skin graft to total pelvic exenteration. Nineteen of the 37 patients are living and well, 13 died as a result of their disease, and another five are living with persistent disease. Among the 18 treatment failures, ten had local recurrence only, while six had distant as well as local recurrence and two had distant metastases without local recurrence. As in all malignancies, early diagnosis and prompt, adequate treatment offer the best opportunity for cure in vaginal cancer.

4572 PROMPT REGRESSION OF CYSTIC VAGINAL ADENOSIS FOLLOWING CESSATION OF ORAL CONTRACEPTIVE THERAPY. (Eng.) Strand, C. L. (Jersey City Medical Center, Jersey City, N.J. 07304); Windhager*, H. A.; Kim, E. H.; Chiranand, N. *Am. J. Clin. Pathol.* 64(4):483-487; 1975.

The cessation of an oral contraceptive (Ovulen-21) was found to result in prompt regression of cystic vaginal adenosis. A 31-yr-old Caucasian woman, gravida 5, para 4, presented with a three-month history of progressive dyspareunia, dysuria, and profuse vaginal discharge. On pelvic examination, the exocervix and entire vagina showed marked reddish discoloration; numerous discrete and ag-

gregated cystic nodules were palpated in the upper two-thirds of the vagina. Laboratory data were within normal values, while culture of the material from the cervix and vagina grew *Escherichia coli*. An electroconization biopsy of the cervix showed numerous nabothian cysts and proliferative endometrium. A vaginal biopsy showed cystic vaginal adenosis. Although no therapy was received for vaginal adenosis, the vaginal discharge diminished and the dysuria disappeared within two months after cessation of oral contraceptive therapy. A repeated biopsy showed only a few pea-sized nodules in the left lateral formix. The regression is considered suggestive of a causal-relationship between long-lasting Ovulen-21 treatment and appearance of a symptomatic type of vaginal adenosis.

4573 PAPILLARY CYSTADENOFIBROMA OF ENDOMETRIUM: A HISTOCHEMICAL AND ULTRASTRUCTURAL STUDY. (Eng.) Grimalt, M. (*Jewish General Hosp., 3755 Cote Ste. Catherine Road, Montreal H3T 1E2 Canada); Arguelles, M.; Ferenczy,* A. *Cancer* 36(1):137-144; 1975.

The light and electron microscopic as well as the histochemical characteristics of a papillary cystadenofibroma of the endometrium are described. The neoplasm arose in the lower uterine segment and was composed of a florid fibroblastic growth arranged in club-shaped papillae projecting into clefts and cystic spaces. The epithelium lining the plicae, recesses, and cysts was exclusively of the mucous-secreting type and bore identical histochemical and subcellular characteristics to that of the normal endocervical epithelium. Essentially similar papillary lesions were previously reported in the endocervix, endometrium, and fallopian tube. The pathogenesis and differential diagnosis of this distinct neoplasm are discussed in the light of the available morphological data. Absence of mitosis is not a reliable criterion for differentiating papillary adenofibroma from low-grade endometrial stromal sarcoma. However, the presence of abundant mitoses in a well-differentiated endometrial stromal cell growth undoubtedly favors sarcoma.

4574 THE INCIDENCE OF YOLK SAC TUMOR (ENDODERMAL SINUS TUMOR) ELEMENTS IN GERM CELL TUMORS OF THE TESTIS IN ADULTS. (Eng.) Talerman, A. (Inst. of Radiotherapy, Postbus 5201, Rotterdam, Holland). *Cancer* 36(1):211-215; 1975.

The incidence of yolk sac tumor (endodermal sinus tumor) elements was studied in 147 germ cell neoplasms of the testis in adults observed over a 4½-yr period. Excluding 79 cases of pure seminoma, yolk sac tumor elements were found in 26 (38%) of 68 tumors; in eight tumors the yolk sac tumor was the predominant element. Yolk sac tumor elements were found admixed with all other germ cell tumor elements. Tumors composed entirely of yolk sac tumor were not encountered. Fifteen (57%) of the 26 patients with tumors containing yolk sac tumor elements have died of their disease during the period under study, compared with 13(31%) of the remaining 42 patients, suggesting that the prognosis of adults with testicular tumors containing yolk sac tumor elements is unfavorable. This is in contrast to the relatively good prognosis of infant and young children with testicular yolk sac tumor, and similar to the prognosis of female patients wit ovarian yolk sac tumor. The results give further s port to the view that yolk sac tumor (endodermal si tumor) is not a distinctive neoplasm of the infant' testis, but a germ cell neoplasm differentiating in the direction of yolk sac or vitelline structures, occurring in the testis, ovary, and extragonadal si in common with other germ cell neoplasms. The find of yolk sac tumor elements in testicular tumors is so of interest in relation to the finding of raised levels of serum alpha fetoproteins (AFP) in some pa tients with germ cell tumors. If yolk sac tumor el ments are responsible for AFP production in patient with germ cell neoplasms, then the finding of yolk sac tumor elements in nearly 40% of testicular germ cell neoplasms, pure seminoma excluded, may explain the high incidence of this association.

4575 POSTPUBERAL CASTRATION AND PROSTATIC CARCINOMA. (Eng.) Egle, N. (Univ. Mainz Medical Sch., 6500 Mainz, West Germany); Altwein*, J. E. *Urology* 6(4):471-473; 1975.

A 60-yr-old man, who had undergone a bilateral inguinal orchiectomy 35 yr earlier, was hospitalized for acute urinary retention. On physical examination, three firm nodules were palpated within a moderately enlarged prostate. Transperineal biopsy revealed a solid, markedly differentiated adenocarcinoma and a retropubic radical prostatectomy was performed. Three yr later the patient was readmitted with local tumor recurrence in the bladder; he died within six months from bilateral ureteral obstruction. Autopsy demonstrated a poorly differentiated adenocarcinoma involving the bladder, prevesical portion of both ureters, and the rectum. Multiple metastases were present in the retroperitoneal lymph nodes, liver, lungs, and pelvis. Nodular hyperplasia of the adrenal cortex was evident. In this patient, plasma testosterone levels measured on each admission were within the upper normal range (1080 ng/100 ml and 940ng/100 ml). This finding, together with the nodular hyperplasia of the adrenal cortex, demonstrated that androgen release from the adrenal glands compensated for the testicular ablation.

4576 CORRELATION OF DIAMETERS OF SECRETORY GRANULES IN CLINICALLY NON-FUNCTIONING CHROMOPHOBE ADENOMAS OF THE PITUITARY WITH THOSE OF NORMAL THYROTROPHS. (Eng.) Gray, A. B. (The London Hosp., London, E1 1BB, England); Doniach*, I.; Leigh, P. N. *Acta Endocrinol. (Kbh.)* 79(3): 417-420; 1975.

Diameters of secretory granules in thyrotrophs and in gonadotrophs were measured in electron micrographs of operation specimens of four normal pituitary glands and of the secretory granules in operation specimens of ten clinically non-functioning chromophobe adenomas. The mean diameter of the thyrotroph granules was 137 ± 26 nm, of the gonadotrophs 204 ± 38 nm, of nine of the ade-

nomas 141 ± 20 nm, and of the remaining adenoma 248 ± 67 nm. There was a significantly ($P < 0.7$) close correlation between granule size in most of the adenomas with that of thyrotrophin granules.

4577 AN INTRAPULMONARY TERATOMA ASSOCIATED WITH THYMIC TISSUE. (Eng.) Day, D. W. (King's College Hosp., Denmark Hill, London SE5 8RX, England); Taylor, S. A. *Thorax* 30(5):582-587; 1975.

A case of benign intrapulmonary teratoma, in which thymic tissue was histologically identified, is presented. A 19-yr-old woman had intermittent pain in the right chest, a cough with purulent sputum, and right-sided pleuritic pain. A chest radiograph showed a round shadow adjacent to the right hilum, which subsequently increased in size. A tuberculin test was positive, and a sputum culture grew commensal organisms only. A right posterolateral thoracotomy revealed a mass in the anterior segment of the right upper lobe; a standard anterior segmental resection was performed. The resected lung segment was an encapsulated, partially cystic mass at one pole, and bronchiectatic at the other. The cystic space of the teratoma was in direct continuity with the distal part of the segmental bronchus. Histologically, the proximal part of the segmental bronchus was lined by normal respiratory epithelium, which showed squamous metaplasia and areas of ulceration in the bronchiectatic segment. The surrounding lung tissue showed lipoid pneumonia, alveoli packed with foamy multinucleated cells, keratinizing stratified squamous epithelium, occasional hair follicles, islets of Langerhans, and areas of smooth muscle and fat. There was a prominent focus of thymic tissue with Hassall's corpuscles at the periphery of the teratoma, from which thin reticulated strands of thymic tissue were traced completely around the teratoma. This is noted as the first reported case of thymic tissue in association with intrapulmonary teratoma.

4578 CLINICAL CONTRIBUTION TO DIFFUSE PLEURAL MESOTHELIOMA. (Ger.) Engelmann, C. (Forschungsinstitut fur Lungenkrankheiten und Tuberkulose, DDR-1115 Berlin-Buch, Karower Str. 11, East Germany); Thamm, W. *Zentralbl. Chir.* 100(5): 266-276; 1975.

Symptomatology, diagnosis, therapy, and etiology of diffuse pleural mesothelioma in 59 patients are described. The male:female ratio was 2:1, and ratio of incidences in the right and left pleura was 1.5:1. The incidence was highest in the sixth decade of life. The average age of the patients was 56 yr for men and 50 yr for women. All patients were ages 31-80 yr. Occupational exposure to asbestos dust for over ten years was established in one patient and exposure to stone dust for over ten years was determined for two patients. Autopsies revealed no indication of asbestosis or silicosis. Pleural affections of the same side (specific pleurities, specific residual empyemic cavity, pneumothorax treatment for lung tuberculosis, exudative pleuropneumonia and thoracic trauma with pleural hemorrhage) were found in the anamneses of 12 patients.

4579 ENDOBRACHYESOPHAGUS AND ADENOCARCINOMA. (Fre.) Savary, M. (Av. Haldimand 19b, CH-1400 Yverdon, Switzerland); Naef, A.-P.; Ozzello, L.; Roethlisberger, B. *Schweiz. Med. Wochenschr.* 105(18):575-579; 1975.

During 6168 esophagoscopies, 164 cylindrical epithelial patches were detected endoscopically with a regular progressive incidence from year to year. This increased detection may be due to improved optics, and the progressive training of endoscopists. The cylindrical epithelial islets of the upper (19%) or lower (4%) esophagus can be distinguished endoscopically from the widespread cylindrical epithelial lining of the lower esophagus (77%). The first type was not associated in any significant manner with any organic pathology. It is of congenital origin usually without pathological significance. Statistically, however, the second type seems to be in the category of peptic esophagitis in its chronic form, and to constitute a form of cicatrization. The incidence (8.8%) of adenocarcinoma of the lower esophagus in association with this second form of cylindrical epithelial lining is significant. It is advisable for peptic esophagitis to be treated before it reaches its chronic stage and, in particular, before the appearance of cylindrical epithelial scars.

4580 ASSEMBLY OF MICROTUBULES ONTO KINETOCHORES OF ISOLATED MITOTIC CHROMOSOMES OF HeLa CELLS. (Eng.) Telzer, B. R. (Dept. Biology, Yale Univ., New Haven, Conn. 06520); Moses, M. J.; Rosenbaum, J. L. *Proc. Natl. Acad. Sci. U.S.A.* 72(10):4023-4027; 1975.

The capacity of HeLa kinetochores to act as preferential sites for the *in vitro* initiation and assembly of tubular subunits into microtubules was investigated. Electron microscopy showed kinetochores to be distinct from the chromatin with which they are associated. When unfixed chromosomes were immobilized by attachment to grids and incubated with chick brain tubulin, microtubules assembled onto the kinetochores. This demonstrated the competence of kinetochores in isolated chromosomes to act *in vitro* as microtubule assembly sites, and suggested that they also possess this capacity *in vivo*. In addition, the results provided a possible means for isolating and characterizing kinetochores.

4581 FAMILIAL NEUROBLASTOMA. (Eng.) Pegelow, C. H. (Los Angeles County--Univ. Southern California Medical center, 1129 N. State St., Los Angeles, Calif. 90033); Ebbin, A. J.; Powars, D.; Towner, J. W. *J. Pediatr.* 87(5):763-765; 1975.

A neuroblastoma was diagnosed in the infant daughter of parents each of whom had a child with neuroblastoma by a previous marriage. Routine and trypsin Giemsa-banded karyotype analysis demonstrated that the patient had cytogenetic abnormalities derived

from each parental line. A number 21p-q- chromosome was found in the proposita, her mother, and maternal grandfather. Examination of this chromosome in prophases that had long chromosomes did not reveal a ring configuration. This atypical number 21 chromosome had a slightly narrower band 21q11. An atypical number 11 chromosome was found in the proposita and her father. Band 11q21 was wide and band 11q23 was narrow. This is apparently the first reported instance of familial neuroblastoma in which trypsin Giemsa-banding was used in chromosomal analysis. The atypical chromosomes and other unusual banding patterns should be explored in instances of neuroblastoma.

4582 VARIED MANIFESTATIONS OF A FAMILIAL LYMPHOPROLIFERATIVE DISORDER. (Eng.)
Fraumeni, J. F., Jr. (Natl. Cancer Inst., A521 Landow Building, Bethesda, Md. 20014); Wertelecki, W.; Blattner, W. A.; Jensen, R. D.; Leventhal, B. G. *Am. J. Med.* 59(1):145-151; 1975.

Immunologic studies were done on a family with diverse forms of lymphoproliferative neoplasia. In a sibship of nine adults, four died of lymphocytic or histiocytic lymphomas, and one of Waldenström's macroglobulinemia (immunoglobulin M [IgM], kappa type) complicated by adenocarcinoma of the lung. In the next generation, one member died of Hodgkin's disease; four of nine healthy persons had impaired lymphocyte transformation *in vitro* in response to phytohemagglutinin-P (PHA-P). Three of these had polyclonal elevations in IgM levels. One had depressed responses to both PHA-P and streptolysin O. Adenocarcinoma of the lung developed in one woman with immune defects, and lymphocytic leukemia developed in her 3-yr-old grandson. This family of Jewish origin migrated from Russia to Massachusetts in 1900. The sibs in generation II had different occupations and lived apart as adults. These findings point to a genetically regulated defect of immunity expressed as diverse lymphoproliferative disorders, including polyclonal and monoclonal IgM gammopathies. The occurrence of pulmonary adenocarcinoma in two members suggests genetic and immunologic determinants in these instances.

4583 CYTOGENETIC STUDIES OF THE SPLEEN IN CHRONIC GRANULOCYTIC LEUKAEMIA. (Eng.)
Spiers, A. S. D. (Royal Hobart Hospital Clinical Sch., Collins St., Hobart, Tasmania 7000, Australia); Baikie*, A. G.; Dartnall, J. A.; Cox, J. I. *Aust. N.Z. J. Med.* 5(4):295-305; 1975.

Cytogenetic studies were performed on splenic tissue from 12 patients with chronic granulocytic leukemia (CGL). The diagnosis had been established by examination of films of peripheral blood and bone marrow aspirate; the stage of the disease varied widely. Six elective splenectomies were performed, as were three for pancytopenia. Splenic tissue was cultured by three methods, metaphases were examined by light microscopy, scored for the presence of Philadelphia chromosome (Ph^1), and the chromosome numbers counted. The disease was in its chronic phase in eight patients, and had been treated with busulphan (seven cases) or splenic irradiation (one case). Small numbers of dividing cells possessing the Ph^1 chromosome were noted in five of those patients. In four patients, chronic granulocytic leukemia had undergone metamorphosis to an acute phase. No dividing cells were observed in two of those patients, while cultures from the other two were Ph^1-positive. The occurrence in the spleen of Ph^1-positive cells possessing additional chromosomal aberrations appeared related to the evolutionary stage of the leukemia process. In the chronic phase of CGL, busulphan treatment appeared to suppress most of the granulocytic cells in the spleen, hence a paucity of Ph^1-positive dividing cells. Poor chromosome morphology with poor optical definition was also common. It is suggested that in advanced CGL, all splenic cells carry the Ph^1.

4584 CHROMOSOMES AND CAUSATION OF HUMAN CANCER AND LEUKEMIA. XII. BANDING ANALYSIS OF ABNORMAL CHROMOSOMES IN POLYCYTHEMIA VERA. (Eng.)
Shiraishi, Y. (*Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14203); Hayata, I.; Sakurai, M.; Sandberg,* A. A. *Cancer* 36(1):199-202; 1975.

The chromosome constitution of bone marrow cells was determined in 13 patients with polycythemia vera (PV). In five of these patients definite karyotypic abnormalities were found: three with 46,XY,Fq-; one with 46,XY,11q-, 13q-; and one with missing Y. The latter cytogenetic finding is thought not to be related to the PV. The three patients with partial deletions of chromosomes had been treated with ^{32}P, and three of them with chemotherapy also. Karyotypes from two of these patients, one with 46,XY,20q-, and another with 46,XY,11q-,13q- were examined with G and/or Q banding. From the results of the banding analysis, it appears that the abnormal chromosomes were due to simple deletions at specific sites on their arms, particularly in the cases with the F abnormality (20q11). The breaks occurred in the regions C11q and D13q. The portions missing from the original chromosomes could not be found on any chromosome. Most patients with PV do not develop chromosomal abnormalities through the course of their disease; when such abnormalities appear (20q- in particular), they seem to result exclusively from radiation (and possibly chemo-) therapy. Thus, cytogenetic changes do not appear to play a crucial role in the genesis of PV.

4585 PH^1-POSITIVE MEGAKARYOBLASTIC LEUKEMIA. (Eng.)
Hossfeld, D. K. (Medical Univ. Clinic, 43 Essen, West Germany); Tormey, D.; Ellison, R. R. *Cancer* 36(2):576-581; 1975.

The case of a 45-yr-old woman with megakaryoblastic leukemia is presented. Megakaryoblastosis and erythrocytic hyperplasia of the bone marrow, thromocythemia, and hepatosplenomegaly were the essential features; 100% of the marrow-derived metaphases were found to be Ph^1-positive. Involvement of all three marrow cell systems (granulocytic, erythrocytic, and megakaryocytic) in the leukemic process was suggested by the marked erythroid hyperplasia ob-

served two weeks prior to admission, the presence of 46.5% megakaryoblasts on the second hospital day, and the subsequent domination of the marrow by myeloblasts and promyelocytes (60-95%). That 100% of the metaphases were Ph^1-positive throughout the course of the disease strongly indicated that all marrow cells were Ph^1-positive and that the causative process leading to leukemia affected the pluripotent stem cell(s).

4586 MYELOMONOCYTIC LEUKEMIA WITH PHILADELPHIA-POSITIVE AND PHILADELPHIA-NEGATIVE CELL LINES IN EARLY CHILDHOOD. (Ger.) Wehinger, H. (Univ.-Kinderklinik, D-7800 Freiburg im Breisgau, Mathildenstr. 1, West Germany); Niederhoff, H.; Bethge, D.; Kunzer, W.; Hoehn, H.; Cohen, G. *Klin. Wochenschr.* 53(9):431-436; 1975.

Myeloproliferative syndrome of the myelomonocytic type in an infant boy is described. The findings fulfilled the criteria for juvenile chronic myeloid leukemia (CML) except that there was no increase of fetal Hb and no depression of RBC carbonic anhydrase I. In one half of the bone marrow cells a Ph^1-chromosome was found. During the course of the disease the Ph^1-positive clone was successively replaced by cell lines with different chromosomal aberrations. This association of hematological and clinical symptoms together with the mixed juvenile-adult CML, suggests a correlation with the cytogenetic mosaicism.

4587 IMMUNOMORPHOLOGICAL STUDIES OF LYMPHOCYTES OF THE PERIPHERAL BLOOD IN PATIENTS WITH CHRONIC LYMPHATIC LEUKEMIA. (Rus.) Andreeva, O. K. (Second Moscow Medical Inst., Moscow, U.S.S.R); Vinogradova, Iu. E.; Grinshpun, L. D.; Lebedev, K. A.; Stenina, M. A. *Vopr. Onkol.* 21(7):43-52; 1975.

Immunomorphological investigations (immune fluorescence test of surface immune globulins, rosette test, phytohemagglutinin-stimulated blast transformation test) of peripheral blood lymphocytes from 36 patients with chronic lymphatic leukemia are described. The leukemic clone was found to originate from the common precursor of T and B lymphocytes. According to the immunological characteristics, three types of chronic lymphatic leukemia were distinguished: T cell type, B cell type, and mixed-cell type. Some 25% of the lymphocytes were able to form rosettes. The percentage of rosette-forming T-lymphocytes was 2-40% in 11 patients. The T-cell type was characterized by normal B-lymphocyte count, reduced surface immunoglobulin concentration, and by considerable increase in the number of lymphocytes capable of spontaneous rosette formation and blast transformation. The B-cell type was characterized by an initially normal B-cell population with reduced surface immunoglobulin concentration on all lymphocytes, by the proliferation of B lymphocytes with reduced surface immunoglobulin level, by normal B lymphocyte count, and by the absence of qualitative and quantitative changes of T lymphocytes. The mixed form featured proliferation of T and B lymphocytes with reduced blast transformation capacity of the proliferating T clone with increase in the B clone with reduced surface immunoglobulin level, by increased rosette-forming T-lymphocyte count, and by reduced blast transformation of T-lymphocytes. When the blast transformation capacity of the proliferating T-clone was normal, and intact B-lymphocytes were absent, proliferation of B-lymphocytes with reduced surface globulin level, absence of B cells with normal surface immunoglobulin concentration, increased rosette-forming T-cell count, and unchanged blast transformation of T-cells were observed.

4588 STUDY OF ACUTE TRANSFORMATION IN 45 CASES OF CHRONIC MYELOID LEUKEMIA. (Fre.) Duhamel, G. (Hopital Saint-Antoine, F 75571 Paris Cedex 12, France); Najman, A.; Gorin, N.; Deloux, J.; Elghouzi, M. *Nouv. Rev. Fr. Hematol.* 15(2): 301-302; 1975.

Clinical, hematological, and biological symptoms of acute transformation were studied in 45 cases of chronic myeloid leukemia. Clinical signs preceded hematological symptoms in two of three cases; changes in general condition were observed in 58%, splenomegaly in 71%, fever in 48%, signs of hemorrhage in 18%, hepatomegaly in 18%, and bone pain in 15%. A hyperleukocytosis above 30,000 was observed in 79%; anemia and thrombocytopenia, however, appeared late and unobtrusively. Leukoblastosis is the main diagnostic criterion; the 20% rate of blood blasts chosen for diagnosis of an acute state was found in 50%. Bone marrow leukoblastosis was found in 80% of the patients. The rise in leukocytic alkaline phosphatase was significant in 80%; chromosomal changes could not be observed. Acute transformation occurred following a chronic phase (average length 38 mo). The acute phase was brief; 20% died one month after its discovery, and 50% died three months later. The therapeutic association of purinethol, methotrexate, and prednisone was compared to that of cytosine and prednisone; complete remission was obtained in only 8% with the first treatment, and did not last over two months. The second association was slightly more successful. Therapy can do very little once the acute transformation occurs.

4589 A SCANNING ELECTRON MICROSCOPIC STUDY OF 34 CASES OF ACUTE GRANULOCYTIC, MYELOMONOCYTIC, MONOBLASTIC AND HISTIOCYTIC LEUKEMIA. (Eng.) Polliack, A. (Sloan-Kettering Inst. for Cancer Res., 410 East 68th St., New York, N.Y. 10021); McKenzie, S.; Gee, T.; Lampen, N.; de Harven*, E.; Clarkson, B. D. *Am. J. Med.* 59:308-315; 1975.

The surface architecture of leukemic cells in 34 patients with acute nonlymphoblastic leukemia was examined. Six patients with myeloblastic, four with promyelocytic, ten with myelomonocytic, eight with monocytic, four with histiocytic, and two with undifferentiated leukemia were studied. Most leukemic histiocytes and monocytes appeared similar and were characterized by the presence of large, well developed broad-based ruffled membranes or

prominent raised ridge-like profiles, resembling in this respect normal monocytes. Most cells from patients with acute promyelocytic or myeloblastic leukemia exhibited narrower ridge-like profiles, whereas some showed ruffles or microvilli. Patients with myelomonocytic leukemia showed mixed populations of cells with ridge-like profiles and ruffled membranes, whereas cells from two patients with undifferentiated leukemia had smooth surfaces, similar to those encountered in cells from patients with acute lymphoblastic leukemia. It appears from the literature that nonlymphoblastic and lymphoblastic leukemia cells (particularly histiocytes and monocytes) can frequently be distinguished on the basis of their surface architecture. The surface features of leukemic histiocytes and monocytes are similar, suggesting that they may belong to the same cell series. The monocytes seem to have characteristic surface features recognizable with the scanning electron microscope and differ from most cells from patients with acute granulocytic leukemia. Although overlap of surface features and misidentification can occur, scanning electron microscopy is a useful adjunct to other modes of microscopy in the study and diagnosis of acute leukemia.

4590 SOME PARAMETERS OF THE PROLIFERATIVE ACTIVITY OF BONE MARROW BLAST CELLS IN PATIENTS WITH ACUTE LEUKEMIA AT DIFFERENT STAGES OF THE DISEASE. (Rus.) Lapotnikov, V. A. (I. P. Pavlov First Leningrad Medical Inst., U.S.S.R.); Nemirovskii, V. S.; Burd, I. E.; Dombrovskaia, N. V. *Probl. Gematol. Pereliv. Krovi* 20(3):24-27; 1975.

The mitotic index and the *in vitro* incorporation of tritiated thymidine (labeling index) in bone marrow blast cells were studied in 36 patients with acute leukemia at different stages of the disease. The labeling index was relatively high before therapy was indicated, but the labeling index of large blasts was significantly lower than that of normal myeloblasts. Cytostatic drug therapy failed to cause any decrease in the labeling index either of the entire blast pool or of blasts with diameters larger than 23 μ. However, the therapy reduced the mitotic index of the leukocytes to 1% against 2.9% as measured before therapy. There was little difference in the labeling index and the mitotic index between untreated patients and patients who were receiving maintenance therapy in remission. However, the total number of thymidine-incorporating leukocytes in the mitotic group (blasts, promyelocytes, myelocytes) was significantly higher than in untreated patients. The increased mitotic index in remission may be due to a blockade of mitoses in the metaphase by vinblastine, or to a prolongation of the mitosis. The labeling index was highest during recurrence (14.2% against 5.2% before therapy and 6.6% in remission), which was primarily due to thymidine incorporation by large blasts. The percentage of DNA-synthesizing small blasts increased to 6.8% aginst 2.5% in untreated patients. These small blasts probably originate from dividing large blasts. The persistence of small blasts in remission can lead to an aggravation of the pathological process.

4591 STRUCTURAL-FUNCTIONAL RELATIONSHIPS IN PLATELETS IN ACUTE LEUKEMIA AND RELATED DI ORDERS. (Eng.) Cowan, D. H. (Cleveland Metrop. Ger Hosp., Ohio); Graham, R. C., Jr. *Ser. Haematol.* 8(1 68-100; 1975.

Platelet ultrastructure and adenine nucleotide metabolism were investigated in patients with acute leukemia to determine mechanisms for the functional defects of platelets. The metabolism of adenine nucle tides was studied using platelets collected by throm bopheresis, using EDTA as anticoagulant, and were se arated by differential centrifugation. After labeli with adenine-8-^{14}C, the platelets were stimulated wi collagen at final concentration 70 μg/ml. Platelets for electron microscopy were obtained by differentia centrifugation from anticoagulated blood. A number structural defects were observed: giant platelets, marked variability in the number and size of cytopla mic granules, dilution of the open channel system, cytoplasmic vacuolization, and a poorly delineated microtubular system. Metabolic defects included reduced cellular concentrations of ATP and ADP and selective reduction of the storage pool (non-metabolic nucleotides. Stimulation of platelets was associate with delayed and incomplete granule migration, reduc degranulation, subnormal release of ATP and ADP, and poor platelet aggregate formation. The structural and metabolic defects indicated that abnormalities exist in the contractile mechanism and in the release reaction of platelets in acute leukemia. Platelets from patients with preleukemic states shared some of the structural and metabolic defects seen in acute leukemia. There was a lesser degree of functional impairment than that seen in more advanced acute leukemia. Studies of megakaryocytic ultrastructure suggest that the structural defects seen in acute leukemia and preleukemia may arise in the late stages of megakaryocyte maturation. The results show that platelets from patients with preleukemic states share some of the structural and metabolic defects seen in acute leukemia, but are less uniformly affected, consistent with the intermediate degree of functional im pairment exhibited.

4592 MACRONUCLEOLAR TRANSFORMATION OF A LEUKEMIC LYMPHOSARCOMA. CLINICAL, MORPHOLOGICAL AND MOLECULAR-BIOLOGICAL PARAMETERS. (Ger.) Seeber, S. (Innere Klinik und Poliklinik, Tumorforschung, Universitatsklinikums, 43 Essen 1, Hufelandstrasse 55, West Germany); Rodenbeck, M.; Brucksch, K.-P.; Schmidt, C.-G. *Blut* 30(1):39-46; 1975.

In a 28-yr-old woman with leukemic lymphosarcomatosis, huge nucleoli developed at a final stage when the patient was refractory to chemotherapy. Cytosine arabinoside plus thioguanine was the last therapy attempted before the patient died with uremia and circulatory collapse. The lymphosarcoma cells were characterized before and after their macronucleolar transformation, by cell fractionation and by characterization of their nuclear 45S RNA fraction after high specific labelling with ^{32}P-ortho-

phosphate. Nucleolar 45S RNA production was markedly increased. Processing of preribosomal RNA did not seem to be blocked.

4593 A FREEZE-ETCH STUDY OF OCCURRENCE OF NUCLEAR PORES IN NORMAL AND TUMOR CELLS. (Eng.) Svejda, J. (Medical Faculty, Univ. J. E. Purkyne, 656 91 Brno, Czechoslovakia); Vrba, M.; Blumajer, J. *Neoplasma* 22(4):385-390; 1975.

A freeze-etch study of nuclear pores was performed on human lymphocytes, epidermal and corneal cells, on Chinese and Syrian hamster embryo fibroblasts, on rat and hamster sarcoma cells, and on cells from a human malignant melanoma. Once produced, the pores did not disappear, and the frequency remained practically the same. The pores were randomly distributed on the nuclear envelope. A rotating method revealed an octa- or nonaedric outside shape of the pores and round inner margin with 8 or 9 granules. One larger granule was found in the center of the pores. The granule was filamentously attached to the margin of the pore. Fibrillar structures running to the pores on the inner surface of nuclear envelope should be examined cytochemically.

4594 ULTRASTRUCTURE OF A HUMAN MALIGNANT IgA-PRODUCING PLASMACYTOMA. (Eng.) Curtis, S. K. (Dept. Anat., East Tennessee State Univ., Johnson City, Tenn. 37601); Propp, R.; Cowden, R. R.; Tartaglia, A. P. *Exp. Mol. Pathol.* 22(3):386-399; 1975.

A rare kind of malignant immunoglobulin A (IgA)-producing plasmacytoma was examined by light and electron microscopy. The plasmacytoma consisted of alternating clusters of two main types of cells; (a) light, rounded cells resembling immature plasma cells with vesicular nuclei, prominent nucleoli, and fairly well developed cytoplasmic organelles; and (b) darker, more differentiated and pleomorphic plasma cells in various stages of development. The lighter cells underwent mitosis and probably gave rise to the darker cells through progressive differentiation. Both types of cells possessed some of the abnormalities observed by other investigators in plasma cells from patients with multiple myeloma and other malignant monoclonal gammopathies, including a tendency for nuclear maturation to lag behind cytoplasmic differentiation. Small membrane-enclosed intranuclear inclusions were observed occasionally in the lighter cells. Other cells included bizarre "giant" cells, immature cells resembling plasmablasts, and macrophages. In addition, the plasmacytoma contained rounded extracellular deposits of a moderately electron-dense material that lacked fibrillar or crystalline organization. The material was osmiophilic, Sudan back B-positive, and moderately well stained with toluidine blue, suggesting that it might have consisted in part of phospholipids. The material failed to stain by the PAS procedure or with eosin suggesting that the deposits did not represent accumulations of immunoglobulins.

4595 HISTOPATHOLOGICAL OBSERVATIONS OF SPONTANEOUS REGRESSION OF ROUS SARCOMAS IN JAPANESE QUAILS. (Eng.) Yoshikawa, Y. (Dept. Measles Virus, Natl. Inst. Health, Musashi-Murayama, Tokyo 190-12, Japan); Yamanouchi, K.; Takahashi, R.; Fujiwara, K. *Jpn. J. Med. Sci. Biol.* 28(3): 189-200; 1975.

Tumors induced in Japanese quails by the Schmidt-Ruppin strain of Rous sarcoma virus, subgroup A, were examined histopathologically. Stock virus was inoculated sc at both wingwebs of 32 quails. At various intervals post inoculation, the quails were necropsied and tumor masses collected and examined. The tumors had reached a maximum size of 11 x 11 mm at day 14; tumor masses were then almost globular, solid, and elastic, reaching to the muscle layers without showing clear boundaries. Most tumors began to regress at 18 days, while some continued to progress. These included five progressing with hematoma, and four progressing without hematoma. Microscopically, three phases of tumor development were noted in regressors. Phase I, days 4-7, involved predominant infiltration of heterophils. Phase II, days 10-14, was characterized by necrosis of tumor cells and focal accumulation of lymphoid cells. In Phase III, days 18-24, tumor cells and heterophils disappeared, small foci of hemorrhage were demonstrated, and plasma cells frequently infiltrated. Microscopic changes in progressors followed a similar pattern. Progressors without hematoma experienced marked growth of tumor cells with characteristic features of typical fibrosarcoma. Hemorrhagic areas surrounded by connective tissues occupied most of the lesions in progressors with hematoma. No marked variation in histologic changes differentiating regressors and progressors were noted in samples taken prior to day 18. In addition, the cellular reaction of the progressors without hematoma had features similar to phase II as late as 24 days, suggesting a lack of cell-mediated destruction of tumor cells supposedly occurring in regressors. It is suggested that progressors with hematoma represent a regressing process which failed to follow the regular course.

4596 WILMS' TUMOR: HISTOLOGIC VARIATION AND PROGNOSIS. (Eng.) Lawler, W. (Dept. Pathology, Stopford Building, The University Manchester M13 9PT, England); Marsden, H. B.; Palmer, M. K. *Cancer* 36(3):1122-1126; 1975.

A histologic analysis of 75 consecutive cases of Wilms' tumor in the Manchester (England) hospital region was carried out to determine whether histologic classification at the time of initial surgery would be helpful in assessing the prognosis. Eight of the tumors could not be histologically classified; the remaining 67 were classified on the presence of tubules, smooth and/or striated muscle, glomerular structures, well-defined nests of typical nephric blastemal cells among a background of mesenchyme, and larger, more open cells with prominent nucleoli. The degree of tubule formation was classified as 0, +, ++, or +++. The 0 group

had no tubules; the + group and ++ groups had definite but scanty tubules; and the +++ group had a very large number of tubules, most tumor cells being involved in tubule formation. Survival time increased with increasing tubule formation; 83% of the +++ group were alive with no sign of recurrence three years after diagnosis, and none of the group 0 patients were alive at this time. With regard to the other features, survival was better when glomerular structures were present than when they were absent, with a small as opposed to a large amount of smooth muscle, and with no cell nests. The presence or absence of larger cells showed no relationship with survival. There was no correlation between age and histological type, and no one histological feature was a significant predictor of prognosis in individual cases. Histological classification was correlated with clinical stage as well as survival, suggesting that the histological classification presented may be very useful in predicting the prognosis of children with Wilms' tumor.

4597 THE GROWTH CHARACTERISTICS OF THE METASTATIC WISTAR/FURTH WILMS' TUMOR MODEL. (Eng.) Murphy, G. P. (Dept. of Experimental Surgery, Roswell Park Memorial Inst., 666 Elm St., Buffalo, N.Y. 14263); Williams, P. D.; Klein, R. *Res. Commun. Chem. Pathol. Pharmacol.* 12(2):397-404; 1975.

Growth characteristics, metastatic spread, and survival times were evaluated in a transplantable Wistar/Furth rat Wilms' tumor model. The tumor doses (1×10^5, 1×10^4, and 1×10^3 live tumor cells/cc per animal) were injected in an attempt to find the optimum level of tumor take. Lung metastases were frequent following tumor injection by all routes. However, tumor spread to the lungs was the least frequent following sc injection of the tumor. Survival time for the im group was statistically longer at all tumor dose levels. For the 1×10^5 tumor dosage, survival time ranged from a mean of 27 days for the intrarenal group to a mean 42 days for the im group. For the 1×10^4 dosage, survival time ranged from a mean of 37 days for the ip group to a mean of 51 days for the im group. It is concluded that this animal tumor closely resembles the human Wilms' tumor, and that the point at which the transplanted tumor fails to be successfully transplanted is below the dosage level of 1×10^3 tumor cells.

4598 GROWTH OF A PLASMA CELL MYELOMA IN LATHYRITIC MICE. (Eng.) Martino, L. J. (St. Louis Univ. Sch. of Medicine, 1402 S Grand Blvd., St. Louis, Mo.); Yeager, V. L.; Taylor, J. J. *Arch. Pathol.* 99(10):536-539; 1975.

The growth of a plasma cell myeloma (Adj PC-5) was studied in 4- to 6-wk-old male and female BALB/c mice made lathyritic by the administration of 1.6% β-aminoproprionitrile (BAPN) in powdered food. The mice received an iv injection of a 0.1-ml cell suspension containing between 10^5 and 10^6 Adj PC-5 cells. Histologic sections of bones from these mice were compared with those from controls fed a normal diet, from mice treated with BAPN alone, and from mice given only tumor cells. Bones from control mice appeared normal. Bones from mice treated with tumor cells and BAPN exhibited histological signs of lathyrism similar to those in mice treated with BAPN only, and of tumor invasion similar to that in the mice treated only with tumor. However, the number of bones in which the medullary cavities were filled with tumor cells was greatly decreased, compared with the number in mice treated with tumor cells only. Additionally, the lathyritic response to BAPN was decreased in tumor-bearing animals, as evidenced by the absence of bone spicules in thickened periosteum and a 50% reduction in the number of epiphyseal rents. The percentage of bones with osteolytic or osteoplastic lesions was the same in the two groups of tumor-bearing animals, as was the number of animals that developed ascites or became paralyzed. The percentage of bones in which tumor cells lifted the periosteum or spread into the muscles through the fibrous periosteum was also the same. In addition to retarding tumor growth in the medullary cavity, BAPN caused osteoporosis and reduced the tensile strength of collagen, both of which allowed extramedullary tumor growth to proceed as usual.

4599 *IN VITRO* CULTURE OF CELLS ISOLATED FROM DIMETHYLNITROSAMINE-INDUCED RENAL MESENCHYMAL TUMORS OF THE RAT. I. QUALITATIVE MORPHOLOGY. (Eng.) Hard, G. C. (Baker Med. Res. Inst., Prahran, Australia); Borland, R. *J. Natl. Cancer Inst.* 54(5):1085-1095; 1975.

The *in vitro* morphology of cells isolated from renal mesenchymal tumors induced in outbred Porton Wistar or inbred Wistar rats by a single ip injection of dimethylnitrosamine (60 mg/kg) was followed in short- and long-term culture. The cells were examined daily by phase-contrast microscopy. The morphology of cells isolated from normal rat-kidney cortex was studied for comparison. Primary tumor-cell isolates consisted of a range of mesenchymal cell forms interspersed between discrete, homogeneous islands of cohesive epithelium-like cells. The latter were presumably derived from renal parenchyma that had been engulfed within the *in vivo* neoplasm by proliferating tumor cells, since this epithelial component did not survive serial subculture. Established tumor cell lines consisted of a pleomorphic range of mesenchymal forms resembling the descriptions of various cell types *in vitro*, including fibroblasts, smooth muscle cells, and endothelial cells. A range of mesenchymal cell forms in culture therefore correlated with the heterogeneous histologic nature of the *in vivo* neoplasm in which fibroblasts, smooth muscle fibers, and endothelium-like cells were also represented. Multinucleate or polymorphonuclear giant cells were characteristic of tumor cell cultures, whereas large, expanded polygonal cells with longitudinal striations were characteristic of normal kidney cell cultures. Some tumor cell cultures were typified by cells with cytoplasmic vacuolation and some by the acquisition of an epithelioid form at high cell

density, a change not preceded by islands of cohesive, epithelium-like cells at preconfluent stages.

4600 FATE OF TERATOCARCINOMA CELLS INJECTED INTO EARLY MOUSE EMBRYOS. (Eng.) Papaioannou, V. E. (Dept. Zoology, Univ. Oxford, South Parks Road, Oxford, U.K.); McBurney, M. W.; Gardner, R. L.; Evans, M. J. *Nature* 258(5530): 70-73; 1975.

In vitro cultures of embryonal carcinoma cells were injected into blastocytes and the rate of development of the blastocytes was determined after transfer to females that subsequently became pregnant. Genetic markers used to distinguish embryonal carcinoma cell progeny from cells of the host embryo were isozymal differences at the glucose phosphate isomerase (GPI) locus (*Gpi-1*), albino or pigmentation, and white-bellied agouti (A^w) or extreme nonagouti (a^c). Cultured embryonal carcinoma cells (C86 or C17) derived from C3H teratocarcinomas were injected into blastocytes obtained by matings of $Gpi\text{-}1^a/Gpi\text{-}1^a$ albino CFLP random-bred mice. Cells of a third line (SIKR-OSB) derived from 129 mice were injected into $Gpi\text{-}1^b/Gpi\text{-}1^b$ blastocytes obtained from matings of a^c/a^c mice of the AG/Cam-derived lethal yellow (A^y/a^e) inbred line. Of the 121 mice born, 11 contained progeny of the embryonal carcinoma cells and four of these were normal healthy animals. The mouse obtained after injection of SIKR-OSB cells had small patches of agouti hair in the coat, indicating the presence of embryonal carcinoma-derived dermal elements interacting in a normal manner in the hair follicles. Three mice obtained after injection of C17 cells exhibited pigmentation in both the coat and eyes; the fourth showed only eye pigmentation. GPI analysis in the one mouse that developed subcutaneous tumors demonstrated the presence of embryoneal carcinoma-derived cells in normal tissue as well as the tumors. None of the six mice obtained after injection of C86 cells had coat or eye pigmentation; however, all six developed one or more subcutaneous tumors, which were classified as poorly differentiated teratocarcinomas. GPI analysis indicated the presence of both embryonal carcinoma-derived and host cells in the tumors. In addition, five of the six animals showed chimerism of macroscopically normal tissue. These results indicate that teratocarcinoma-derived embryonal carcinoma cells from *in vitro* cultures can participate in normal morphogenesis and differentiation when restored to the environment of the early embryo.

4601 ULTRASTRUCTURAL STUDIES OF PARALLEL TUBULAR ARRAYS IN HUMAN LYMPHOCYTES. (Eng.) Brunning, R. D. (Univ. Minnesota Health Sci. Cent., Minneapolis); Parkin, J. *Am. J. Pathol.* 78(1):59-70; 1975.

4602 ELECTRON MICROSCOPIC STUDY OF HYALINE INCLUSIONS (PSEUDOPSAMMOMA BODIES) IN MENINGIOMAS [abstract]. (Eng.) Kepes, J. J. (Univ. Kansas Med. Cent., Kansas City, Kansas). *J. Neuropathol. Exp. Neurol.* 34(1):92; 1975.

4603 SCANNING ELECTRON MICROSCOPY OF NORMAL AND ABNORMAL EXFOLIATED CERVICAL SQUAMOUS CELLS. (Eng.) Murphy, F. (Dept. Obstet. Gynaecol., Univ. Birmingham, England); Allen, J. M.; Jordan, J. A.; Williams, A. E. *Br. J. Obstet. Gynaecol.* 82(1):44-51; 1975.

4604 BRONCHIAL CARCINOID TUMOR WITH LIVER METASTASES AND FLUSH SYNDROME. ULTRASTRUCTURAL STUDY. (Fre.) Patricot, L.-M. (Hopital de la Croix-Rousse, F. 69317 Lyon, Cedex 1, France); Vauzelle, J.-L.; Leung, T.-K; Feroldi, J. *Arch. Anat. Pathol.* 23(1):5-13; 1975.

4605 CARCINOGENESIS STUDIES ON HUMAN BRONCHIAL EPITHELIUM (BE) [abstract]. (Eng.) Trump, B. F. (Univ. Maryland, Baltimore, Md. 21201); Barrett, L. A.; McDowell, E. M. *Proc. Am. Assoc. Cancer Res.* 16:59; 1975.

4606 FAMILIAL BRONCHIAL CARCINOID AND POLYENDOCRINE ADENOMATOSIS. (Fre.) Dry, J. (Hopital Rothschild, 43, bd de Picpus, F 75571 Paris Cedex 11, France); Lebrigand, H.; Pradalier, A.; Leynadier, F.; Huguier, M. *Ann. Med. Interne (Paris)* 126(6/7): 491-496; 1975.

4607 DEVELOPMENT OF MALIGNANCY DURING METHOTREXATE TREATMENT. (Heb.) Schewach-Millet, M. (Haim Sheba Medical Center, Tel Hashomer, Israel); Feinstein, A.; Rafael, D. *Harefuah* 88(8): 366-367, 400; 1975.

4608 LEIOMYOSARCOMA OF SUPERFICIAL SOFT TISSUE WITH UNUSUAL METASTASIS. (Eng.) Kaplan, G. (Veterans Administration Hosp., New York, N.Y.); Varga, P. *N.Y. State J. Med.* 75(12):2240-2241; 1975.

4609 ELIMINATION OF INDUCED CHROMOSOME ABERRATIONS IN EMBRYOGENESIS OF MICE [abstract]. (Eng.) Buselmaier, B. (Institut fur Anthropologie und Humangenetik Universitat Heidelberg, Neuenheimerfeld 328, West Germany); Hansmann, I. *Mutat. Res.* 29(2):215-216; 1975.

4610 CHROMOSOME OBSERVATIONS IN C57Bl STRAIN LEUKEMIC MICE. (Fre.) Leonard, A. (Departement de Radiobiologie, Centre d'Etude de l'Energie nucleaire, B-2400 Mol, Belgique); Maisin, J. R.; Mattelin, G. *C. R. Soc. Biol. (Paris)* 169(2): 464-467; 1975.

4611 MITOTIC ANOMALIES AS THE SOURCE OF MUTATION OF THE GENOME: POLYPLOIDIZATION CYCLES--SEGREGATION IN MAMMALIAN CELL POPULATION. (Eng.) Rizzoni, M. (Centro di Studio di Genetica Evoluzionistica del C.N.R. and Istituto di Genetica, Universita di Roma, Rome, Italy); Spirito, F.; Perticone, P.; De Salvia, R.; Ricordy, R.; Tanzarella, C.; Palitti, F. *Mutat. Res.* 29(2):200-201; 1975.

4612 IDENTIFICATION OF CHROMOSOMAL ABERRATIONS OBSERVED IN HUMAN CANCER CELLS BY R BANDING. (Fre.) Ayraud, N. (Laboratoire de Cytogenetique, U.E.R. de Medecine et Centre Antoine Lacassagne, 06000 Nice, France). *C. R. Soc. Biol. (Paris)* 169(2): 365-373; 1975.

4613 SEX-CHROMOSOME LOSS IN HUMAN TUMOURS. (Eng.) Zankl, H. (Dept. Human Genetics, Univ. Saarland, 6650 Homburg/Saar, West Germany); Seidel, H.; Zang, K. D. *Lancet* 1(7900):221; 1975.

4614 SIMULTANEOUS OCCURRENCE OF HIATUS HERNIA AND CARCINOMATA IN THE CARDIA AND THE ESOPHAGUS. (Dan.) Nilsson, T. (laege, Plantagevej 14, DK-3460 Birkerod, Denmark); Halkier, E. *Ugeskr. Laeger* 137(4):199-201; 1975.

4615 INTESTINAL LYMPHANGIECTASIA AND TUMOR SPREAD BY REVERSAL OF LYMPHATIC FLOW IN ASSOCIATION WITH A CARCINOMA OF THE COLON. (Fre.) Debray, C. (Hopital Bichat, 170, bd Ney, F 75877 Paris Cedex 18, France); Leymarios*, J.; Marche, C.; Malmonte, A. M.; Le Canuet, R. *Nouv. Presse Med.* 4(33):2391-2392; 1975.

4616 NEOPLASTIC PANETH CELLS: OCCURRENCE IN AN ADENOCARCINOMA OF A MECKEL'S DIVERTICULUM. (Eng.) Scharfenberg, J. C. (Alton Ochsner Med. Found. Clin., New Orleans, La.); DeCamp, P. T. *Am. J. Clin. Pathol.* 64(2):204-208; 1975.

4617 CARCINOID SYNDROME. (Fle.) Carpentier, J. (Evergemse Steenweg, 154, 9030 Wondelgem, Belgium); Brys, R.; De Keyser, R. *Tijdschr. Gastroenterol.* 18(2):100-105; 1975.

4618 CANCER IN CROHN'S DISEASE -- DANGER OF A BY-PASSED LOOP. (Eng.) Greenstein, A. J. (Mt. Sinai Sch. Med., City Univ. of N.Y., Fifth Ave. & 100th St., New York, N.Y. 10029); Janowitz, H. D. *Am. J. Gastroenterol.* 64(2):122-124; 1975.

4619 PRIMARY HEPATIC MALIGNANCY IN PREGNANT WOMEN. (Eng.) Purtilo, D. T. (Univ. Massachusetts Medical Sch., 55 N. Lake Ave., Worcester, Mass. 01604); Clark, J. V.; Williams, R. *Am. J. Obstet. Gynecol.* 121(1):41-44; 1975.

4620 MULTIPLE LYMPHANGIOENDOTHELIOMA OF THE SPLEEN IN A 13-YEAR-OLD GIRL. (Eng.) Hamoudi, A. B. (Children's Hosp., Columbus, Ohio 43205); Vassy, L. E.; Morse, T. S. *Arch. Pathol.* 99(11):605-606; 1975.

4621 PRELEUKEMIAS. (Ger.) Schott, G. (I. Med. Klinik, 95 Zwickau, Karl-Keil-Strasse 35, East Germany). *Z. Gesamte Inn. Med.* 30(4):159-161; 1975.

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4625 LEUKEMIC MITOCHONDRIA. III. ACUTE LYMPHO BLASTIC LEUKEMIA. (Eng.) Schumacher, H. R. (Harrisburg Hosp., Pa.); Szekely, I. E.; Fisher, D. R. *Am. J. Pathol.* 78(1):49-58; 1975.

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4627 CULTURE OF LEUKEMIC CELLS. II. NEW ACHIEVEMENTS IN CYTOGENETICS OF CHRONIC MYELOID LEUKEMIA. (Pol.) Rozynkowa, D. (Inst. Clinical Pathology, Medical Acad., Lublin, Poland); Stepien, J. *Pol. Arch. Med. Wewn.* 54(1):39-45; 1975

4628 CONTRIBUTION TO THE STUDY OF NEUROLOGICAL MANIFESTATIONS OF CHRONIC LYMPHATIC LEUKEMIA. ROLE OF ASSOCIATED GLOBULIN ABNORMALITIES. A DESCRIPTION OF 8 CASES. (Fre.) Masson, R. (Service d'Hematologie, Hopital Edouard-Herriot, Lyon, France); Boucher, M.; Joyeux, O.; Chazot, G.; Martin, C.; Favre-Gilly, J.; Revol, L. *Rev. Neurol. (Paris)* 131(6):373-385; 1975.

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4630 GENETIC HETEROGENEITY IN FAMILIAL BREAST CANCER [abstract]. (Eng.) Lynch, H. T. (Creighton Univ., Omaha, Nebr.); Guirgis, H. A.; Mulcahy, G.; Lynch, J.; King, M. C.; Maloney, K.; Thul, P.; Thomas, R. *Proc. Am. Assoc. Cancer Res.* 16:190; 1975.

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4632 DIFFERENTIATED TUMOR CELL CLONES OF THE CENTRAL NERVOUS SYSTEM [abstract]. (Ger.) Wechsler, W. (Koln, West Germany). *Zentralbl. Allg. Pathol.* 119(3):227; 1975.

4633 CORRELATION BETWEEN CELLULAR REPAIR DEFICIENCY AND HIGH INCIDENCE OF SKIN CANCER IN XERODERMA PIGMENTOSUM [abstract]. (Jpn.) Takebe, H. (Dept. Fundmtl. Radiol., Fac. Med., Osaka Univ., Osaka, Japan); Akiba, H. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 23.

4634 A POSSIBLE PRIMARY CUTANEOUS CARCINOID. (Eng.) van Dijk, C. (Patholog, Anat. Laborat., Wilhelmina Gasthuis, le Helmersstraat 104, Amsterdam, The Netherlands); ten Seldam*, R. E. J. *Cancer* 36(3):1016-1020; 1975.

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4637 LEIOMYOMA OF VESICOVAGINAL SEPTUM CAUSING URINARY RETENTION. (Eng.) Brown, R. C. (Univ. of Iowa Hosp. and Clinics, Iowa City, Iowa 52242); Hawtrey, C. E.; Rose, F. *Urology* 6(3):379-381; 1975.

4638 ON TWO TYPES OF MALIGNANT NEOPLASM OF GENITALS AND MAMMARY GLANDS. (Ukr.) Voitenko, V. P. (Inst. Gerontology, Acad. Sciences, Ukrainian S.S.R.). *Dopov. Akad. Nauk Ukr. RSR Ser. B* (1):79-80; 1975.

4639 ENDOMETRIAL STROMAL TUMOR IN A CHIMPANZEE. (Eng.) Toft, J. D., II (USAF Sch. Aerospace Medicine, Brooks Air Force Base, Tex. 78235); Mac Kenzie, W. F. *Vet. Pathol.* 12(1):32-36; 1975.

4640 LYMPHATIC OBSTRUCTION IN CARCINOMATOUS ASCITES. (Eng.) Feldman, G. B. (Natl. Cancer Inst., Bethesda, Md.). *Cancer Res.* 35(2): 325-332; 1975.

4641 ADRENAL MEDULLARY HYPERPLASIA IN FAMILIAL MEDULLARY THYROID CARCINOMA [abstract]. (Eng.) DeLellis, R. A. (New England Med. Cent. Hosp., Boston, Mass.); Wolfe, H. J.; Gang, D. L.; Gagel, R. F. *Am. J. Pathol.* 78(1):40a; 1975.

4642 CLASSIFICATION OF MALIGNANT TUMORS OF THE THYROID GLAND ACCORDING TO THE WHO 1974 NOMENCLATURE. HISTOLOGICAL VERIFICATION OF 327 CASES OF MALIGNANT TUMORS OF THE THYROID GLAND. (Ger.) Neracher, H. (Institut fur Pathologische Anatomie, Kantonsspital, CH-8091 Zurich, Switzerland); Hedinger*, C. *Schweiz. Med. Wochenschr.* 105(32): 1000-1006; 1975.

4643 PATHOLOGY OF THYMOMAS -- SELECTED TOPICS. (Pol.) Mioduszewska, O. (Instytut Onkologii, Wawelska 15, 02-034 Warszawa, Poland). *Nowotwory* 25(1):7-14; 1975.

See also:

* (Rev): 4208, 4219, 4220, 4221, 4222, 4223, 4224, 4235, 4240, 4254, 4255, 4256, 4257, 4258, 4259, 4260, 4261
* (Chem): 4270, 4295, 4296, 4305, 4306, 4308, 4312, 4331, 4332, 4339, 4355
* (Phys): 4362
* (Viral): 4400
* (Immun): 4468, 4504, 4514, 4515, 4525, 4537, 4544, 4547
* (Epid-Biom): 4646, 4649, 4650, 4652, 4655, 4660, 4661, 4672

4644 MORTALITY DUE TO MALIGNANT NEOPLASMS, AUSTRALIA, 1950-1972 -- A SUMMARY OF TRENDS AT THE MAJOR SITES. (Eng.) Scott, G. (Dept. Preventive and Social Medicine, Univ. Sydney, Sydney, Australia). *Cancer Forum* (5):250-255; 1975.

The trends in mortality in Australia from the leading sites of malignant neoplasms were studied for 1950-1972 by means of Standardized Mortality Ratios. Until the establishment of the NSW Central Cancer Registry in 1972, no population-based cancer incidence data was available in Australia. Hence it is difficult to determine whether the trends in mortality are related to changes in incidence. Sites included in the tables of Standardized Mortality Ratios are: digestive organs plus peritoneum; stomach; large intestine; rectum; pancreas; and lung. In these tables data for males and females are presented separately. Tables for females only include breast, cervix, corpus, and ovary; and for males, prostate. There has been a significant decline in mortality from gastric cancers in both male and female accompanied by a rise in mortality from malignant tumors of the pancreas. Mortality from cervcial cancer has apparently declined despite problems of classification and coding of cancers of the female genital organs. Incidence and mortality from lung cancer have risen sharply. Mortality and incidence appear to be slowly increasing for ovarian cancer, Hodgkin's disease, and leukemia.

4645 CANCER IN FINLAND 1953-1970: INCIDENCE, MORTALITY, PREVALENCE. (Eng.) Teppo, L. (Finnish Cancer Registry, The Institute for Statistical and Epidemiological Cancer Research, Finland); Hakama, M.; Hakulinen, T.; Lehtonen, M.; Saxen, E. *Acta Pathol. Microbiol. Scand.* [A] *Supplement 252* :1-66; 1975.

Data relating to the incidence, mortality, and prevalence of cancer and of tumors of selected sites in Finland from 1953 to 1970 is presented. The information was compiled by the Finnish Cancer Registry -- The Institute for Statistical and Epidemiological Cancer Research and the Childhood Cancer Registry. Some facts are presented about Finland, the organization of the Registry, and of the material and definitions used in this study. The specific sites for which data are presented are: lip, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, larynx, lung, breast, cervix, uterus, ovary, testis, prostate, kidney, urinary bladder, skin, thyroid gland, and brain. In addition, information concerning Hodgkin's disease, leukemia and childhood cancers is presented. There were 28,414 new cases of cancer diagnosed in males and 26,375 cases in females between 1966 and 1970. Lung, stomach, and prostate (30.9, 14.6, and 8.3%, respectively) were the leading types of cancer in males, while breast, uterus, and stomach (18.8, 13.0, and 12.2% respectively) predominated in females. The incidence rates of cancer of the lung, larynx, and stomach were much higher among Finnish men than for men of Denmark, Sweden, and Norway. However, the incidence rates of breast, prostate, colon, and rectum were comparatively low in Finland. Cancer of the esophagus was characterized by a relatively high incidence in females, while the incidence of testicular cancer was among the lowest in white populations of the world. The incidence rates of cancer the stomach and esophagus decreased from 1953 to 1970 in both sexes, all age groups, and nearly all parts of the country. In contrast, the rates for cancer of the pancreas, colon, and rectum were increasing. There was a steady increase in lung canc among males, but only a slight increase in females. The incidence of breast cancer increased continuously, attributable to the postmenopausal age group of women, while cancer of the cervix decreased, probably due to the large-scale mass-screenings for detection of precancerous lesions. Cancer incidenc of the corpus uteri and prostate increased. The in creasing and decreasing trends of the various cance types compensated each other, resulting in an almos unchanged trend in the total cancer incidence for both sexes.

4646 MALIGNANT MELANOMA OF THE SKIN IN BLACK AFRICANS. (Eng.) Giraud, R. M. A. (Baragwanath Hosp., Johannesburg, South Africa); Rippey, E.; Rippey, J. J. *S. Afr. Med. J.* 49(16): 665-668; 1975.

Black patients with histologically confirmed malignant melanoma came to Baragwanath Hospital in Johannesburg between 1959-1970. There was a distinct female preponderance in this study but particularly in the older age groups (70 years & above). The majority of melanomas are found on the sole of the foot and on the palm of the hand. Areas most at risk are of unstable pigmentation in otherwise lightly pigmented areas. Of the cases studied, 23% gave a history of a pre-existent pigmented mole at the site of the melanoma. The low survival rate (3-5 yr) may be due to the high incidence of melanoma in the elderly. There is no statistically significant correlation between the diameter of the lesion and the patient's prognosis. Therapy included surgery (with or without block dissection of lymph nodes), intraarterial chemotherapy, deep x-ray therapy, immunotherapy and vaccinica inoculation.

4647 PATTERN OF SECONDARY ADRENAL TUMORS IN IBADAN, NIGERIA. (Eng.) Ejeckam, G. C. (Univ. Ibadan and Univ. Coll. Hosp., Ibadan, Nigeria); Attah*, E. 'B. *Int. Surg.* 60(6/7):368-369; 1975.

The pattern of secondary adrenal tumors was studied in Ibadan over an eight yr period and found to be totally different from that in Western countries. Among 82 secondary adrenal tumors in all age groups, from 840 cases of cancer, Burkitt's tumor accounted for 30 cases followed by "other malignant lymphomas" (13 cases) and Wilms' tumor (9 cases). Carcinomas of the cervix and breast rarely metastasized to the adrenal.

4648 PRIMARY CEREBRAL NEOPLASIA IN RHODESIA. (Eng.) Levy, L. F. (Harari Cent. Hosp., Salisbury, Rhodesia); Auchterlonie, W. C. *Int. Surg.* 60(5):286-292; 1975.

Rhodesia, consisting mainly of low income Africans and middle class Europeans, provided an excellent area for the study of diseases in developed and underdeveloped populations. Of 6,505 neurosurgical procedures undertaken during a 17-yr period, 62% were performed on African patients and 38% on Europeans, despite the fact that the African population exceeds the European population by 20 times. Life expectancy for Africans is lower than for Europeans. Primary cerebral neoplasia and vascular disorders appear more commonly in persons over 50. Direct comparison between the European and African populations is impossible. There were 205 primary intracranial neoplasms seen in Africans, and 244 in Europeans. In African workers, there were 28-33% reported meningiomas in contrast to 15.3-20.5% of Caucasians. There was no significant difference in the incidence of pituitary tumors or craniopharyngiomas. Acoustic neuromas are rare in Africans. In this series, supratentorial astrocytomas accounted for 24% of African brain tumors compared to 45% in Europeans. A comparison of the incidence of gliomas indicated that no genetic factor is involved. The average age in all tumor groups except medulloblastomas and midline cerebellar astrocytomas is approximately 15 yr lower in African patients. Results of treatment are inferior in African patients because African patients delay treatment until tumor is far advanced. Many of these patients also suffer from concomitant diseases and poor health.

4649 EARLY CARCINOMA OF THE STOMACH IN EUROPE. 1170 CASES FROM THE 1968-1973 PERIOD. (Ger.) Miller, G. (Chirurgische Klinik des Burgerspitals, Ch-4500 Solothurn, Switzerland); Kaufmann, M. *Deutsch. Med. Wochenschr.* 100(39):1946-1949; 1975.

The incidence of early carcinoma of the stomach was assessed in a retrospective study of 317,816 gastroscopies performed between 1968 and 1973. Among 18,887 gastric carcinomas there were 1,170 early carcinomas. Endoscopic typing of 564 cases revealed that 22% were Type I, 29% Type IIa or IIb, 25% IIc, and 24% Type III (Japanese classification). Of early carcinomas, 47% were located in the lesser curvature. The diagnosis was made by biopsy in 90% of cases. The correctness of biopsy was proportional to the number of biopsies per lesion. Adding cytological examination to biopsy decreased the number of false-negative results by 30%. In most cases the history was non-specific. But in 70 patients (16%) over 40 yr-old, gastro-intestinal bleedings were the reason for endoscopic examination and led to the diagnosis of early carcinoma. The frequency of discovery of early carcinomas/100 gastroscopies varied markedly in different countries: Greece had the highest incidence (4.27%) and Finland the lowest (0.05%). The average for all the European countries was 0.38%, compared to 0.88% reported for Japan.

4650 THE INCIDENCE OF MALIGNANCIES IN TRANSPLANT RECIPIENTS. (Eng.) Penn, I. (Univ. Colorado Sch. Medicine, Denver, Colo.). *Transplant. Proc.* 7(2):323-326; 1975.

De novo cancers were encountered in 27 (5.6%) of 483 renal-homograft recipients followed for up to 11.5 yr. Clinical features of *de novo* malignancies were studied in a series of 234 patients, of whom 231 received kidney transplants, 2 received hearts, and 1 a liver transplant. Among the 241 malignancies that developed, there were 95 cancers of the skin and lips, 66 solid lymphomas, 18 carcinomas of the uterine cervix, 12 carcinomas of the lung, and 50 miscellaneous malignancies. The patients with lymphomas differed from those with other cancers in that they were slightly younger (34.9 *vs* 39.6 yr), the tumors occurred earlier after transplantation (20.6 *vs* 31.6 mo), were more frequently treated with antilymphocyte globulin (40% *vs* 25.4%), and more often received organs from unrelated donors (7.6% *vs* 65.4%). Only 11% of the lymphoma patients are alive at present compared with 82% of those with carcinomas of the skin, lips, or uterine cervix and 25% of patients with other types of cancers. The development of cancer could not be related to any individual immunosuppressive measure but appeared to be a result of immunosuppression in general. Preexisting neoplasms may have been present in two donors and in 22 recipients. Presumably the malignancies present at time of transplantation were small but grew rapidly under the influence of immunosuppressive therapy. The incidence of *de novo* cancer in organ-transplant recipients is not high enough to contraindicate the performance of transplantations, particularly as many of the neoplasms are of low-grade malignancy and are easily controlled with conventional cancer therapy. In the case of high-grade neoplasms, consideration should be given to reducing, or even stopping, immunosuppressive therapy. Recovery of the lymphoreticular system has been observed in several patients treated in this manner.

4651 INCIDENCE OF MALIGNANT TUMORS IN U.S. CHILDREN. (Eng.) Young, J. L., Jr. (Natl. Cancer Inst., Bethesda, Md.); Miller, R. W. *J. Pediatr.* 86(2):254-258; 1975.

Incidence rates of childhood cancer in the United States from 1969 through 1971 were determined in the Third National Cancer Survey, designed by the Biometry Branch of the National Cancer Institute. The survey was conducted in seven metropolitan areas (Detroit, Minneapolis-St. Paul, Pittsburgh, Atlanta, Birmingham, Dallas-Fort Worth, and San Francisco-Oakland), as well as in the states of Iowa and Colorado. In these areas, 1,925 malignant tumors were diagnosed in white children under age 15 yr, 225 in black children, 16 in other nonwhites, and 7 with race not specified. The annual incidence rates for all malignant tumors were 124.5/million whites and 97.8/million blacks. These rates were, respectively, 63% and 84% higher than the corresponding annual mortality rates, 1960-1969. The

rank order of the seven most common malignat tumors in childhood was unchanged when measured by incidence or by mortality rates: (1) leukemia, (2) tumors of the CNS, (3) lymphoma, (4) neuroblastoma, (5) Wilms' tumor, (6) bone cancer, and (7) rhabdomyosarcoma. The data for whites were generally in accord with past experience, except for the seemingly high frequency of malignant carcinoid. Five carcinoid-type bronchial adenomas were diagnosed in children aged 10-13 yr. Among blacks, there was an unexplained deficiency of CNS tumors in males. Only 14 males were affected compared with 41 black females, although 1960-1969 mortality data for children gave CNS tumors as the cause of death in 509 black males *versus* 499 females. Since this survey was population based and had a nearly complete ascertainment of cases, it provides the best estimate yet of rates of childhood cancer in the United States.

4652 CLINICAL ASPECTS OF CARCINOMA OF THE LIVER. (Eng.) Frey, P. (Departement fur Innere Medizin der Universitat, Kantonsspital, CH-8091 Zurich, Ramistr. 100, Switzerland); Schmid, M.; Knoblauch, M. *Dtsch. Med. Wochenschr.* 100(32):1625-1629; 1975.

The incidence and diagnosis of epi-cirrhotic liver carcinoma was studied. Between 1969 and 1973 there were 84 cases of primary liver carcinoma and 467 of cirrhosis among 10,211 autopsies. In 74 the carcinoma developed in a cirrhotic liver. Clinically the diagnosis of carcinoma was made in 14 cases. The mean survival time after the diagnosis was seven wk; after onset of the terminal symptoms 13 wk. Typical clinical features were decompensated, hypertrophic, often coarsely granular, liver cirrhosis. The best diagnostic method was laparoscopy and determination of α_1-fetoprotein and cholestatic enzymes.

4653 ^{99m}Tc-PERTECHNETATE THYROID SCINTIGRAPHY IN PATIENTS PREDISPOSED TO THYROID NEOPLASMS BY PRIOR RADIOTHERAPY TO THE HEAD AND NECK. *(Eng.)* Arnold, J. (Michael Reese Hosp. & Medical Center, 2900 S. Ellis Ave., Chicago, Ill. 60616); Pinsky, S.; Ryo, U. Y.; Frohman, L.; Schneider, A.; Favus, M.; Stachura, M.; Arnold, M.; Colman, M. *Radiology* 115(2):653-657; 1975.

The possibility that radiotherapy to the thymus of infants might predispose to the development of thyroid neoplasms was investigated. Histories, physical examinations and ^{99m}Tc-pertechnetate imaging were used to evaluate 1,452 persons who had had x-ray therapy to the neck region for benign conditions 18-35 yr previously. Thyroid imaging was begin 20-30 min after iv administration of 5 mCi ^{99m}Tc sodium pertechnetate. Thyroid abnormalities were found in 301 patients (21%) and thyroid malignancy was found in 29% of 193 patients with abnormal studies who were explored surgically. Thyroid imaging detected 96% of these abnormalities, 40% of which would not have been unequivocally established by physical examination alone. Nuclear imaging could not distinguish benign from malignant lesions.

4654 RISK INDICATORS IN CHILDHOOD MALIGNANCIES (Eng.) Salonen, T. (Finnish Cancer Regis try, Univ. of Helsinki, Finland); Saxen, L. *Int. J Cancer* 15(6):941-946; 1975.

A series of 972 childhood malignancies was compared with a control series of healthy children matched f date and place of birth. Several variables were tested for possible etiological significance. The information was obtained from the Finnish Cancer Re gistry and from the antenatal records of the mother The data themselves can be considered reliable and may therefore be useful in the compilation of large series from different sources. No significant asso ciations were found between the various types of ma lignancies and the variables studied. In the group consisting of all malignancies, a risk ratio of 2.0 could be significantly excluded for most variables. In the leukemia group, both pelvic X-ray and polio vaccination were associated with slightly elevated risk ratios, but the differences between this group and the matched controls were not statistically significant. BCG vaccination was performed during the perinatal period in 90% of the children, but the pro portion was the same in the study and control groups the hypothesis that this vaccination confers protection was not supported.

4655 INFANT LEUKAEMIAS AND COT DEATHS. (Eng.) Stewart, A. (Dept. Social Medicine, Univ. Birmingham, Birmingham, England). *Br. Med. J.* 2(5971):605-607; 1975.

A comparison between infant deaths from leukemia and cot deaths is reported. In the 1-5 mo age group, which accounts for less than 3% of childhood leukemias, there were more girls (71) than boys (66), of 137 studied, who died of leukemia; more summer (43) than winter (27) deaths; and over twice as many deaths among January to June births (94), than among July to December births (43). Cot deaths among the same age group (1-5 mo) have not decreased in frequency since the discovery of antibiotics, and they affect boys (220) more than girls (148); are commoner in winter (127) than in summer (59); and have a peak incidence at this age of 1-5 mo in 368 cases studied.

4656 INCIDENCE OF ORAL CANCER WITH PARTICULAR REFERENCE TO HARD PALATE CANCER IN 1 MILLION POPULATION IN THE DISTRICT OF VISAKHAPATNAM. (Eng.) Reddy, C. R. R. M. (Andhra Medical Coll., Visakhapatnam-530 002, India); Prahlad, D.; Ramulu, C. *Indian J. Cancer* 12(1):72-76; 1975.

A study was made of the frequency of oral carcinomas in different parts of India. This article concerns Visakhapatnam, an area chosen for the study due to the high incidence of hard palate carcinoma found there. There were 93 oral carcinoma patients registered, as a yearly average, in the hospitals of Visakhapatnan, India. The annual incidence rate was 9.12/100,000. Over 57% of these oral carcinomas were from hard palate

as it is the commonest oral carcinoma of either sex. Women had more oral carcinomas than men, the ratio being 3.2. Although the habit of chewing tobacco is uncommon in Visakhapatnam, there is wide prevalence of reverse smoking (inhalation) of home made cigars (Chuttas). There is a statistically significant relationship between inhalation and carcinoma of hard palate in females.

4657 SMOKING AND DISEASE: EFFECT ON SERUM ANTITRYPSIN IN HOSPITALIZED PATIENTS. (Eng.) Rees, E. D. (Univ. Kentucky Coll. Medicine, Albert B. Chandler Medical Center, Lexington, Ky. 40506); Hollingsworth, J. W.; Hoffman, T. R.; Black, H.; Hearn, T. L. *Arch. Environ. Health* 30(8):402-408; 1975.

Serum anti-tryptsin was selected as a biochemical marker to be used in an epidemiologic study assessing some possible effects of smoking on hospitalized medical patients. The mean serum antitrypsin (AT) activity for 1,829 patients hospitalized with medical problems exceeded the mean for a group of blood bank donors by 51%. Analysis of data from individual patients in terms of the general category (there were 16) of their disease and smoking status (smoker, nonsmoker, former smoker) indicated significant differences due to disease status and smoking status. The highest mean AT levels were associated with infectious, respiratory, and neoplastic diseases. Smokers had significantly higher mean levels than nonsmokers, and lung cancer patients had significantly higher mean levels than those with other malignant neoplasms. Among smokers (as a group) mean AT levels, though elevated relative to nonsmokers were not significantly related to duration or intensity of smoking; but former smokers showed a decline with time following cessation of smoking in their mean AT level to the mean level for nonsmokers. These findings provide further evidence of the sensitivity of serum antitrypsin activity to environmental influences.

4658 EXPERIENCE FROM A BREAST CANCER SCREENING CENTER. (Eng.) Letton, A. H. (No affiliation given); Wilson, J. P.; Lamis, P. A. *Am. Surg.* 41(10):620-625; 1975.

Preliminary statistics from a breast cancer screening center in Atlanta, Ga. are presented. Among 7,082 asymptomatic women screened, 39 cancers were found (a rate of 5.5/1,000). Twenty-six percent of the cancers found were noninvasive, and 7.6% had metastasis to the axillary nodes; 18 of the patients had palpable masses, while 37 women had malignancies that were visualized by xerography. Fifteen percent of the cancer patients had a positive thermogram. A total of 62.06% of the patients with cancer had calcification in the malignancy, and 5.1% had bilateral malignancies. Details of the screening program included a medical history, physical examination, xerography, and biopsy. The dilemma of visualization of minimal breast cancer was discussed from the prospectives of the radiologist, surgeon, and pathologist. Various localization and surgical techniques were proposed, and modified radical mastectomy with removal of the breast and axillary nodes is supported as the necessary present approach.

4659 THE AMERICAN BURKITT LYMPHOMA REGISTRY: A PROGRESS REPORT. (Eng.) Levine, P. H. (Natl. Cancer Inst., Bethesda, Md. 20014); Cho, B. R.; Connelly, R. R.; Berard, C. W.; O'Conor, G. T.; Dorfman, R. F.; Easton, J. M.; DeVita, V. T. *Ann. Intern. Med.* 83(1):31-36; 1975.

Demographic and clinical features of 114 patients confirmed by the American Burkitt Lymphoma Registry in its first three years of operation are presented and compared with known features of African Burkitt's lymphoma. In addition, the survival data up to December, 1973 are reviewed. The registry includes information on incidence, presenting features, clinical course, epidemiological aspects, and laboratory parameters. The tumor shows a general predilection for incidence in the jaw, gonads, gastrointestinal tract, and CNS in both American and African patients, but incidence of bone marrow and peripheral lymphoma is higher in American patients. Response to chemotherapy was found to be similar in both groups. Epidemiologic features that appear to link American and African Burkitt's lymphoma, such as fewer cases in high-altitude areas and clustering of patients in time and space, require more study. The absence of the Epstein-Barr virus genome in African and American cases raises the possibility that agents other than this virus may be responsible for inducing some cases of the disease on both continents.

4660 CLINICO-EPIDEMIOLOGICAL CHARACTERISTICS OF LYMPHOGRANULOMATOSIS. (Rus.) Plotnikov, Iu. K. (1st Dept. of Hosp. Therapy, D. I. Ul'ianov Kuibyshev Medical Inst., USSR). *Ter. Arkh.* 42(6):56-60; 1975.

Clinico-epidemiological observations of 239 patients, with lymphogranulomatosis diagnosed during the 1965-1973 period were compared with observations of 790 persons in a control group. There were no statistically significant differences in the occupational distribution, even though the percentage of workers employed in the petrochemical and lacquer industries and of those exposed to engine exhaust gases was somewhat but insignificantly higher among the patients than in the control group. Angina with subsequent tonsillectomy was 1.8 times more frequent among patients than in the control, however, the difference was significant statistically. The incidence of penumonia, cholecystitis, otitis, dysentery, etc., was considerably higher among the patients (15.7% against 9.6%). The incidences of gastric and duodenal ulcer, chronic gastritis, uterine fibromyoma, adenoma of the prostate gland, intestinal polyps, chronic eczema, psoriasis and bronchial asthma were largely the same in the two groups during the last four years preceding the diagnosis of lymphogranulo-

matosis of the epidemiological survey. During the same period, the incidence of chronic inflammatory diseases, such as cholecystitis, otitis, pneumonia of stage II and III, tonsillitis, pyelonephritis and colitis was 12.9% among patients against 7.6% in the control. The incidence of malignant tumors was 1.8 times more frequent among closest relatives (parents, brothers and sisters) of the patients than among those of the control subjects. The findings indicate the possible role of earlier and concurrent inflammatory and pyegenic processes in the development of lymphogranulomatosis, i.e., that the latter may be preceded by immunological disturbances.

4661 ACUTE NONLYMPHOCYTIC LEUKEMIA. AN ADULT CLUSTER. (Eng.) Bartsch, D. C. (942 Lowry Medical Arts Bldg., 350 St. Peter St., St. Paul, Minn. 55102); Springher, F.; Falk, H. *J.A.M.A.* 232(13):1333-1336; 1975.

Between 1970 and 1973, seven cases of acute nonlymphocytic leukemia (five cases of acute myelomonocytic leukemia and two cases of acute myelocytic leukemia) were diagnosed in the village of Elmwood, Wisconsin, and the surrounding area. The patients ranged in age from 14-97 yr. Interpersonal relationships were noted among all patients in the group. This cluster of cases represents a greater than 20-fold increase in the expected incidence of this disease for this population. Morphologic similarities in the blast cells were seen in all cases; these included abundant cytoplasm, with small amounts of azure granulation, and nuclei that often showed soft folding and convolutions. This cluster of cases may bear a relationship to bovine leukemia because the town was located in dairy farming country and because a number of the patients had either worked at or lived near the town creamery.

4662 PLUTONIUM FALLOUT IN TOKYO. (Eng.) Miyake, Y. (Geochemistry Res. Assoc., Tokyo, Japan); Katsuragi, Y.; Sugimura, Y. *Pap. Meterol. Geophys.* 26(1):1-8; 1975.

The monthly fall rates of plutonium 239 and 238 in Tokyo during the period from Jan. 1967 to the end of 1973 are reported. The cumulative amounts of plutonium fallout in Tokyo from the beginning of nuclear explosions to the end of 1973 are estimated to be 1.2mCi/km^2 and 55 μCi/km^2, respectively, for plutonium 239 and 238. Owing to the accidental release of 238 due to a satellite failure, the ratio of 238 to 239 increased abruptly from 1.8% in 1966 to 16% in 1967. The maximum value of the ratio, 31%, was observed in 1970, and then the value decreased gradually to 6.3% in 1973. The ratio of 239 to Sr-90 during the period of 1968 to 1973, in which the Chinese bomb tests prevailed, was about 1%, which was lower than the former value of 1.6% in the tests conducted by the USA and the USSR. The total amounts of deposition in the northern hemisphere of 239 and 238 were calculated to be about 200 kCi and 9 kCi, respectively. Of the 9kCi of plutonium, 2 kCi was of satellite origin.

4663 LEUKEMIA: OCCUPATIONAL CHEMICAL FACTORS. (Eng.) Vigliani, E. C. (Clinica del Lavo "L. Devoto" dell'Universita di Milano, Milano, Ital *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 248-252.

A number of cases of leukemogenesis due to occupational benzene exposure are reviewed. An estimatio of the available literature indicates that the numb of known cases of leukemia attributed to benzene is at least 150. Benzene leukemia has been seen in fa tories where there were outbreaks of benzene poison such as rotogravure plants and shoe manufacturers before benzene was banned as a solvent for inks and glues. Benzene leukemias are mostly acute, hemocyt blastic or myeloblastic. Leukemia often develops i subjects with longstanding benzene-induced hypore- generative anemia or pancytopenia and constitutes t terminal stage of the disease. Aplastic anemia occu generally in subjects while they are still exposed to high concentrations of benzene; leukemia may occu at the same time, or shortly after cessation of expo sure. At least 20 cases of acute erythroleukemia ha been reported. During the period 1964-1970, among 142 Italian workers with chronic benzene poisoning, 16 deaths occurred; three of these from aplastic anemia and 13 from leukemia, all of them acute, hemo cytoblastic. In a retrospective study of severe hem pathies seen in Lyon hospitals, a history of exposur to benzene and/or its homologues in the preceding 10 yr was found in a significantly higher proportion of patients with acute leukemia, chronic lymphocytic leukemia and aplastic anemia, than among control patients; this was not the case for chronic myeloid leukemia and other blood disorders. It is concluded that clinical as well as epidemiological data are indicative of a strong leukemogenic action of benzen in man, the leukemia being mostly acute and hemocyto blastic or myeloblastic in type, occurring directly or superimposed on aplastic changes in the bone marrow, and that the possibility exists that benzene might also induce chronic types of leukemia. Mechanisms by which benzene might induce leukemia are not clarified but the following possibilities are considered: 1) somatic mutation; 2) activation of a latent leukomogenic virus; and 3) induction of an immune impairment. It might also be that more than one mechanism is involved in benzene leukemogenesis and that various coincidental factors may be required for leukemia to occur.

4664 A POSSIBLE POPULATION MONITORING SYSTEM ON ENVIRONMENTAL MUTAGENS: STATISTICAL STUDIES ON RETINOBLASTOMA IN JAPAN. (Eng.) Sugahara, T. (Dept. Experimental Radiology and Ophthalmology, Kyoto Univ., Kyoto, Japan); Uyama, M. *Mutat. Res.* 30(1):137-142; 1975.

To determine the rate of somatic mutation in human populations, the incidence of retinoblastoma in Japan was studied using data from four university hospitals (total cases studied: 97 unilateral and 43 bilateral, recorded from 1965-1974). Three

separate methods of analysis were performed using the patient's age at diagnosis: I. a comparison of the means and variances assuming normal distribution for bilateral and unilateral cases separately; II. an examination of cases plotted on a semi-logarythmic scale with one- and two-hit curves for unilateral and bilateral cases separately; and III. a calculation of the changes in the probability of affecting one eye with age. Method I showed a decrease in the mean age at diagnosis for unilateral cases which became statistically significant when the date were pooled. Analysis of bilateral cases showed a significant difference between Kyoto and Kyushu. For method II the fitting of a two-hit curve was not good, perhaps because of the small number of cases. In bilateral cases the slope of a linear regressed line was in inverse proportion to the expected somatic mutation rate per year. Method III yielded a rather constant probability up to 20 mo of age at four hospitals (0.67), but at two the probability decreased from 0.84 at 5 mo of age to 0.65 and 0.59 at 20 mo. All three methods revealed different distribution patterns for bilateral retinoblastoma at different hospitals. The influence of a common carcinogen, the food preservative furylfuramide, together with regional diet viarations, was advanced to explain the higher early probability of retinoblastoma calculated for the two variant hospitals. Because of the low hereditary rate, it was suggested that an increase in the mutation rate is responsible for the rising incidence of this disease.

4665 THE SEARCH FOR AN ENVIRONMENTAL CARCINOGEN IN THE ETIOLOGY OF ESOPHAGEAL CANCER IN THE CASPIAN LITTORAL OF IRAN. (Eng.) Mahboubi, E. (Univ. Nebraska Medical Center, Omaha Nebraska); Kmet, J.; Salmasizadeah, S. *Proc. Int. Cancer Congr. 11th*, Vol. 3 *(Cancer Epidemiology, Environmental Factors)*. Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 253-257.

A search for an environmental carcinogen in the etiology of esophageal cancer was undertaken in the Caspian littoral of Iran where areas of high and low incidence are only a short distance apart. Analyses were carried out for nitrosamines, nitrates and nitrites; polynuclear aromatic hydrocarbons; and aflatoxins in food samples. A wide range of foodstuff samples of cooked meals and their ingredients were collected from one village in both the high and low incidence areas. The water in the households from which the food samples were taken was also analyzed. Ten to 12 food samples per household were collected (60-80/village) and a total of 120 water samples. Consideration was also given to cultural, ethnic and religious differences which might have some bearing on the etiology of esophageal cancer. The main stable food item in Iran's high esophageal cancer incidence area was bread, while that in the low incidence area was rice. The intake of green vegetables, and vitamins A, C, and riboflavin was low in the high incidence area. In the low incidence area, most nitrosamine concentration values were less than 3 ppb. In a village in the high incidence area, high values of 15.5 ppb dimethylnitrosamine and 1.5 ppb diethylnitrosamine were found in a dish containing rice, spinach and yogurt. These findings of nitrosamines in food samples from the high incidence area were not, however, confirmed by mass spectrometry. The nitrate level in the water samples was within international standards. Ninety-five percent of the water samples had nitrite concentrations within normal limits, and in 5% no nitrite was found. It is concluded that no recognized exposure to any exogenous carcinogens was found and no single factor responsible for the high incidence of esophageal cancer in the Caspian littoral of Iran was identified. It is suggested that a combination of factors connected with climate, rate of precipitation, soil, vegetation and agriculture plus socio-economic level and cultural habits might be responsible for the differences in incidence of esophageal cancer in the two regions studied.

4666 INFERENCES FROM DATA: DEVELOPMENT OF MATHEMATICAL MODELS. (Eng.) Wagner, G. (German Cancer Res. Center, Heidelberg, West Germany); Tautu, P. *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors)*. Florence, Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 11-17.

Mathematical models previously developed for the epidemiology of non-infectious diseases are examined, and new models utilizing the latest theoretical, observational and experimental knowledge are suggested. Relationship between cancer incidence and age has been studied frequently, but the voluminous incidence data collected in the last 15 yr does not reveal the nature of the cancer process. There are no mathematical models providing etiologic or causal factors in cancer. Even the existence of a causal relationship between smoking and lung cancer is still open to discussion. Special statistical models have been developed to determine if leukemia cases cluster in time and space which would be termed structural models. A single mathematical model for the genetic contribution in cancer is not possible because of the multiple aspects involved in the cell division process. An illness-death stochastic model describing the relapse, recovery and death of cancer patients has been devised. All the previously mentioned models are "data-reduction" models or mathematical forms for an observed distribution of data capable of submission to significance tests. "Data-generating" models would incorporate the following characteristics: (1) knowledge of the natural history of the cancers; (2) the "taxonomic" adjacency relation based on a particular index of similarity, e.g. genetic or immunogenetic and the "biotic" adjacency relation which assumes common environmental or sociocultural factors; (3) mathematical description of the whole carcinogenisis process with formulation of a system of events contributing to the process. The age-incidence curve would actually be the age-specific failure rate or age at which tumor developed as result of failure of individual to over-

come contributing pathogenic events; (4) distribution of etiological factors and end results of their interaction into two sets and establishment of many-one correspondences between the two sets. This system is static and for continous process relationships, the two sets of elements must be represented as two parallel systems of multiple events. The "data-generating" mathematical model attempts to explain the process and suggest new experiments and observations.

4667 AN IMPROVED SEMI-QUANTITATIVE METHOD FOR THE ESTIMATION OF AFLATOXIN M_1 IN LIQUID MILK. (Eng.) Patterson, D. S. P. (Central Veterinary Lab., Weybridge, Surrey, KT15 3NB, England); Roberts, B. A. *Food Cosmet. Toxicol.* 13(5):541-542; 1975.

An improved method for the estimation of aflatoxin M_1 in milk eliminates the risk of emulsion formation, reduces the working time for analysis prior to thin-layer chromatography, and increases the sensitivity of analysis to 0.1 μg/l of milk. The method involves mixing liquid or reconstituted powdered milk with acetone (100 ml) and then transferring it to a dialysis sac. The latter is allowed to equilibrate overnight in a Kilner or similar jar containing 66% aqueous acetone. The dialysis sac is then drained into the jar and the toxin is extracted from the diffusate with chloroform (at least 250 ml). The extract is passed through a bed of anhydrous Na_2SO_4 as are two further extracts obtained with 50 ml chloroform. Following evaporation of the combined chloroform extracts, the residue is redissolved in 50-300 ml chloroform, depending on the likely level of aflatoxin M_1 contamination. The semiquantitative estimation of aflatoxin M_1 in the extract is carried out by visual matching under UV light. Silica-gel-coated thin-layer plates are used and chromatograms are developed with chloroform-acetone-propan-2-ol. The detection limit of 0.1 μg/l compares favorably with that of the more elaborate procedure of Schuller et al and is the level of sensitivity currently required for prospective milk surveys.

4668 THE INCREASING INCIDENCE OF BREAST CANCER IN SASKATCHEWAN. (Eng.) Barclay, T. H. C. (Allan Blair Memorial Clinic, Saskatchewan Cancer Commission, Regina, Saskatechewan, Canada); Black, M. M.; Hankey, B. F.; Cutler, S. J. *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 282-288.

A study was conducted to determine if the reported increase in breast cancer in Saskatchewan was real or only apparent. Factors which may be responsible for an apparent increase in incidence rates and which were investigated in this study were an improvement in the case finding program, changes in the age distribution within the population, and shifts in diagnostic criteria. In Saskatchewan, there is a case finding program in the form of a comprehensive cancer diagnostic and treatment service which is available to all residents. In addition, all tissue removed at all surgical procedures, must be examined by an experienced pathologist. Pathology reports wit a cancer annotation and copies of all death certificates are made available to the Cancer Commission. These sources are used to identify patients with mali nant disease, who are not referred to the clinic. A retrospective study, using all the available source of information concerning the diagnosis of breast cancer in Saskatchewan indicated that the observed increase in incidence rate between 1946-1972 was not due to improved case finding in the later years. During this period of time the age distribution of the female population in Saskatchewan did change. An increase was evident in all 5-yr age groups, except 35-39 yr (in which no material change occurred). The annual number of patients with breast cancer rose over this span of 27 yr from 132 to 331. After the influence of age change was eliminated, there was still an increase of 57% in the incidence rate. It was considered possible that the changes in incidence rate might be explained by differences in interpretation of the histology of tumors by the pathologists Available original histology slides from women who ha been diagnosed in 1946, 1951, 1960, and 1968 as havin mammary cancer and from women with benign breast tumo seen in the same years were re-evaluated in a blind study. For the entire series of 469 malignant tumors, there was considerable agreement between the original and the revised diagnoses. The small differences whic did exist indicated that cancer of the breast was overdiagnosed by the pathologists in the earlier thre selected years. In the re-examination of 423 benign lesions, only one invasive cancer was found and four tumors diagnosed as benign were seen to exhibit *in situ* carcinomatous change. It is concluded that the increase in the incidence of breast cancer over the past 27 yr is real.

4669 HEPATOCELLULAR CARCINOMA AND THE HEPATITIS B VIRUS: DETECTION OF ANTIBODY TO HEPATITIS B CORE ANTIGEN. (Fre.) Maupas, P. (Lab. de Virologie, Faculte de Medecine et de Pharmacie, 2 bis, boulevard Tonnelle, 37000 Tours, France); Larouze, B.; Saimot, G.; Payet, M.; Werner, B.; O'Connell, A.; Millman, I.; London, W. T.; Blumberg, B. S. *Nouv. Presse Med.* 4(27):1962-1964; 1975.

4670 PROSTATIC TUMORS IN IRAN. (Eng.) Habibi, A. (Churchill Ave., Tehran, Iran); Manouchehri, A.; Diba, M. H.; Sajadi, M.; Ghavam, M. *Int. Surg.* 60(8):405-407; 1975.

4671 ANALYSIS OF SURVIVAL AND RECURRENCE VS. PATIENT AND DOCTOR DELAY IN TREATMENT OF BREAST CANCER. (Eng.) Dennis, C. R. (Downstate Med. Cent., Brooklyn, N.Y.); Gardner*, B.; Lim, B. *Cancer* 35(3):714-720; 1975.

4672 TUMORS OF THE SUBMAXILLARY AND SUBLINGUAL SALIVARY GLANDS. (Spa.) Carrasco Presilla, J. A. (Hospital Vargas, Caracas, Venezuela); Luongo Font, J. E. *Arch. Hosp. Vargas, Caracas* 17(1/2):91-110; 1975.

4673 HORMONES, BODY BUILD AND ENDOMETRIAL CANCER [abstract]. (Eng.) de Waard, F. (Dept. Epidemiology, Inst. Social Medicine, Univ. Utrecht, The Netherlands). *Acta Cytol. (Baltimore)* 19(5): 486-487; 1975.

4674 POSITIVE CERVICAL SMEARS--PREDISPOSING FACTORS AND FOLLOW-UP [abstract]. (Eng.) Macgregor, J. E. (Univ. Aberdeen, Aberdeen, Scotland). *Acta Cytol. (Baltimore)* 19(5):483; 1975.

4675 MEASUREMENT OF THE FREE FRACTION IN A LABORATORY-SCALE URANIUM MINE. (Fre.) Duport, P. (Commissariat a l'Energie Atomique, France); Madelaine, G.; Renoux, A. *Chemosphere* 4(5):283-288; 1975.

4676 PROPOSED TOLERANCE FOR AFLATOXIN IN PEANUTS. (Eng.) Wessel, J. R. (No affiliation given). *Manuf. Confect.* 55(1):28, 32-35; 1975.

4677 AFLATOXIN M_1: OCCURRENCE IN STORED AND FRESHLY HARVESTED CORN [abstract]. (Eng.) Shotwell, O. L. (Northern Regional Res. Lab., Agricultural Res. Service, U.S. Dept. Agriculture, Peoria, Ill. 61604); Goulden, M. L.; Hesseltine, C. W. *Cereal Foods World* 20(9):442; 1975.

4678 GAS-CHROMATOGRAPHIC DETERMINATION OF POLYCYCLIC AROMATIC HYDROCARBONS IN WASTEWATER. (Rus.) Shushunova, A. F. (Gor'kii State Univ., Gor'kii, U.S.S.R.); Shkodich, P. E.; Shkanakin, N. G.; Lembik, Zh. L. *Gig. Sanit.* (8):61-62; 1975.

4679 THE KINETIC ANALYSIS OF THE CELLS STARTING DNA REPLICATION IN THE SYSTEMS STIMULATED TO PROLIFERATE. II. THE THEORETICAL BASIS OF THE METHOD. (Rus.) Zorin, A. V. (Inst. Biophysics Ministry of Public Health of the U.S.S.R., Moscow, U.S.S.R.); Isanin, N. A.; Iakovlev, A. Iu. *Tsitologiia* 17(7):776-782; 1975.

4680 CARCINOGENESIS AND RADIATION RISK: A BIOMATHEMATICAL RECONNAISSANCE. (Eng.) Mayneord, W. V. (7 Downs Way Close, Tadworth, Surrey, KT20 5DR, England); Clarke, R. H. *Br. J. Radiol.* (Suppl. 12):1-112; 1975.

4681 CONSIDERATIONS FOR THE CALCULATION OF CANCER INCIDENCE [abstract]. (Jpn.) Ishibe, T. (Nara Medical Coll., Kashihara-City, Japan); Tsubura, Y. *Gann, Proc. Jpn. Cancer Assoc., 34th Annual Meeting, October 1975.* p. 27.

4682 CANCER PATTERNS IN AUSTRALIA: 1950-1973. (Eng.) Gray, N. (Anti-Cancer Council of Victoria, Melbourne, Australia). *Proc. Int. Cancer Congr. 11th.* Vol. 3 *(Cancer Epidemiology, Environmental Factors).* Florence, Italy, October 20-26, 1974. Edited by Bucalossi, P.; Veronesi, U.; Cascinelli, N. New York, American Elsevier, 1975, pp. 191-200.

See also:

* (Rev): 4203, 4205, 4206, 4208, 4209, 4210, 4211, 4217, 4237, 4238, 4240, 4257, 4262, 4263, 4264, 4265
* (Chem): 4291, 4305, 4309, 4310
* (Phys): 4364, 4366, 4371
* (Viral): 4434
* (Immun): 4467, 4515
* (Path): 4570

4683 ESTABLISHMENT AND SOME BIOLOGICAL CHARACTERISTICS OF HUMAN HEPATOMA CELL LINES. (Eng.) Doi, I. (Okayama Univ. Medical Sch., Shikatacho 2-5-1, Okayama 700, Japan); Namba, M.; Sato, J. *Gann* 66(4):385-392; 1975.

Two cell lines of human hepatoma, HLE and HLF lines, were established *in vitro* from the hepatocellular carcinoma of a 68-yr-old man. One clone (HLEC) was obtained from a single HLE cell. The cells of HLE and HLEC were epithelial-like and both of these cells demonstrated glycogen granules in the cytoplasm when stained with periodic acid and Schiff reagent. Although HLF cells resembled fibroblasts in morphology, they appeared to have originated from hepatoma cells, judging from epithelial characteristics in aggregates reconstituted by rotation culture and heterotransplantability. HLE cells produced α-fetoprotein until day 187 of culture, but HLF cells did not produce α-fetoprotein at any period examined. The chromosome number of both cell lines was distributed near the triploid range. HLF cells were transplantable into the cheek pouch of adult Syrian hamsters treated with cortisone acetate (5 mg ip, one day before and three days after implantation), but HLE cells were not. The absence of α-fetoprotein production in HLF cells suggests either that they were derived from hepatoma cells not producing α-fetoprotein, or that they may have lost the capacity to produce α-fetoprotein *in vitro*.

4684 NON-MENDELIAN SEGREGATION IN HYBRIDS BETWEEN CHINESE HAMSTER CELLS. (Eng.) Harris, M. (Dept. Zoology, Univ. California, Berkeley, Calif. 94720). *J. Cell. Physiol.* 86(2/-Suppl. 1/Part II):413-429; 1975.

Mechanisms of segregation in hybrids between Chinese hamster cells (272 and 599) were studied using clonal analysis. Hybrid cells were grown in HAT medium and subjected to back selection with bromodeoxyuridine (BUDR) or azaguanine (AZG). In AZG or BUDR at 30 μg/ml, segregation began with a random, high-frequency event that gave rise to cells capable of growth in both HAT and back selection medium, unlike the precursor hybrid or original parental cell types. BUDR-resistant segregants were propagated serially in the presence of BUDR, and were examined by clonal analysis for changes in plating properties during long term culture. During 240 days the HAT/BUDR plating ratio for segregant cells declined continuously, from approximately ten down to 10^{-6}. A parallel decrease was observed in the rate of H^3-thymidine incorporation, along with a drop in thymidine kinase activity. These shifts took place only in the presence of BUDR, and were reversed by altered selection in HAT medium. Clonal studies showed that the evolution of segregant properties occurred in most cells, and did not arise from variation and selection of minority cell types. These properties of the segregating system are not consistent with models based on gene mutation, chromosome rearrangements, or chromosome loss. The evolution of segregants resembles more closely a sorting-out progress, taking place by intracellular selection over many generations. The segregating units may be cytoplasmic determinants linked functionally to nuclear genes, which modulat phenotypic expression.

4685 CONCURRENT DEVELOPMENT OF RESISTANCE TO 6-AZAURIDINE AND ADENOSINE IN A MOUSE CELL LINE. (Eng.) Hashmi, S. (Coll. Physicians and Surgeons, Columbia Univ., New York, N.Y.); May, S. R.; Krooth, R. S.; Miller, O. J. *J. Cell. Physiol.* 86(2/Suppl. 1/Part I):191-200; 1975.

A variant of the hypoxanthine-guanine phosphoribosyltransferase-deficient, and adenine phosphoribosyltransferase-deficient mouse A9 cell line was obtained by selecting cells resistant to 6-azauridine These cells were not only resistant to 6-azauridine (5×10^{-4} M), but also to adenosine (10^{-3} M). Resistance persisted indefinitely, even in the absenc of both compounds. The resistant cells were killed by 5-fluorouridine (10^{-6} M), indicating that the part of the salvage pathway for pyrimidine ribonucleotide biosynthesis which is relevant to the action of 6-azauridine was intact. The heritable change producing concurrent resistance to 6-azauridine and adenosine probably involves the *de novo* pyrimidine biosynthetic pathway.

4686 CONTROL OF NORMAL DIFFERENTIATION OF MYELOID LEUKEMIC CELLS: VIII. INDUCTION OF DIFFERENTIATION TO MATURE GRANULOCYTES IN MASS CULTURE. (Eng.) Fibach, E. (Dept. Genetics, Weizmann Inst. Science, Rehovot, Israel); Sachs, L. *J. Cell. Physiol.* 86(2/Suppl. 1/Part I):221-230; 1975.

The behavior of the three types of myeloid leukemic cells; IR^+D^+, IR^+D^-, and IR^-D^-; and the properties of mature granulocytes induced from myeloid leukemic cells are described. IR^+D^- cells were induced to differentiate to granulocytes in mass culture in liquid medium by conditioned medium (CM) from cultures of lungs from ICR mice injected with endotoxin. About 90% of the leukemic cells were induced to differentiate, 50% to mature granulocytes and 40% to intermediate stages. An efficient induction granulocyte differentiation was also obtained with CM from primary cultures of CR rat embryo or human spleen (from four patients with Hodgkin's disease) and there was a lower activity with CM from various other sources. IR^+D^- cells were induced to differentiate to about 20% cells with intermediate stages, but not to mature granulocytes; IR^-D^- cells could not be induced to differentiate to intermediate or mature stages. IR^+D^+ cells were induced to form intermediate stages of granulocyte differentiation, to phagocytose and to attach to the surface of the Petri dish, three days after incubation with CM. Optimum induction of mature granulocytes required six more days incubation with CM. Mature granulocytes induced from leukemic cells showed cytochemical properties and a morphology in the electron microscope similar to that of normal mature granulocytes. These induced granulocytes did not form leukemia in animals or colonies in

agar. The granulocytes induced from the myeloid leukemic cells, therefore, behave like normal mature granulocytes.

4687 CORRELATED SUPPRESSION BY 5-BROMODEOXYURIDINE OF TUMORIGENICITY AND PLASMINOGEN ACTIVATOR IN MOUSE MELANOMA CELLS. (Eng.) Christman, J. K. (Mt. Sinai Sch. Med., New York, N.Y.); Silagi, S.; Newcomb, E. W.; Silverstein, S. C.; Acs, G. *Proc. Natl. Acad. Sci. USA* 72(1):47-50; 1975.

C_3471 mouse melanoma cells derived from B_559 cells by culturing in medium with 1 mg/ml 5-bromodeoxyuridine (BrdU) were compared to the parent line for release of plasminogen activator. Plasminogen activator was determined indirectly by plasmin's ability to release ^{125}I-labeled fibrin degradation products from [^{125}I]fibrinogen-coated petri dishes. Dishes to which 10^6 cells were plated in medium supplemented with fetal bovine, mouse, rabbit, or dog serum, containing 100,000 counts/min (cpm) [^{125}I]fibrinogen. After 18 hr incubation, the parent line released 27,390 cpm, 50,310 cpm, 32,730 cpm, and 63,870 cpm from fetal bovine, dog, mouse, and rabbit sera resp., while C_3471 cells released 0, 0, 0, and 2,670 cpm from the same respective sera. When 10^6 cells were incubated in sera-free medium for 18 hr and the medium was assayed for plasminogen activator using dog plasminogen and [^{125}I] fibrin as substrate, B_559 cells released 140,000 cpm/10^6 cells, while C_3471 cells released an undetectable amount. Exposure of B_559 cells to BrdU (3 μg/ml) for 48 hr resulted in 1,400 cpm/10^6 cells/24 hr exposure; this as compared to 23,000 cpm/10^6 cells with no exposure and to 22,500 cpm/10^6 with 72 hr exposure and subsequent replating to cultures without BrdU. When 10^6 B_559 cells grown with 3 μg/ml BrdU were injected s.c. into C57BL/6J mice, 0-30% tumorigenicity resulted (100% control tumorigenicity). This compared to cells which were grown with 3 μg/ml BrdU for 48 hr, replated, and grown for five days without BrdU which had 100% tumorigenicity. The capacity of BrdU to reversibly inhibit both the expression of plasminogen activator and of tumorigenicity in B_559 melanoma cells suggests that these two properties may have more than a chance association and that the malignant state reflects the expression of one or more specialized gene products.

688 MAPPING OF THE G_1 PHASE OF A MAMMALIAN CELL CYCLE. (Eng.) Naha, P. M. (Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, U. K.); Meyer, A. L.; Hewitt, K. *Nature* 258(5530): 49-53; 1975.

Temperature-sensitive variant clones of BALB/3T3 cells were put on a linear time scale map by measuring their time of entry into S phase. The variants accumulated cells in G_1 during incubation at the restricted temperature (38 C) so the cells were delayed in entering S. To identify possible biochemical alterations in the nuclei of variants at the restricted temperature, two clones that were widely separated on the time scale map of G_1 were grown for 16 hr at 38 C and their nuclear proteins then analyzed by polyacrylamide gel electrophoresis. Both variant clones contained a unique protein which double labeling experiments indicated was a nonhistone protein. Cells labeled with ^{14}C-methionine and ^{3}H-tryptophan showed a high rate of incorporation of tryptophan, which is incorporated selectively into nonhistone proteins. The results indicate that temperature-sensitive cells could be a useful tool for study of the control of the cell cycle in mammalian cell systems, particularly in the identification of endogenous components necessary for regulation of cell growth.

4689 DIFFERENCES IN THE UREA-EXTRACTED OR FIBROUS PROTEINS OF MOUSE EPIDERMIS AT VARIOUS STAGES OF MALIGNANT TRANSFORMATION. (Eng.) Carruthers, C. (Dept. of Immunology Res., Roswell Park Memorial Inst., Buffalo, N.Y. 14203); *Oncology* 30:125-133; 1974.

The differences in the urea proteins or mouse epidermis at various stages of neoplastic transformation are described. The urea-extractable proteins of normal and hyperplastic epidermis, papilloma, and squamous-cell carcinoma were fractionated by gel filtration on Sepharose 4B columns to yield excluded and retarded urea protein fractions. There was a considerable difference in the elution patterns of the urea protein of normal epidermis and carcinoma. The level of excluded proteins decreased from normal epidermis through hyperplastic epidermis, papilloma, and carcinoma; retarded protein fractions increased proportionately. The urea proteins of normal and hyperplastic epidermis had consistent elution patterns, whereas papilloma and carcinoma were less consistent, but still comparable. Normal epidermis showed a large sharp peak of proteins excluded by Sepharose 4B and a broad peak for the retarded fractions; carcinoma urea proteins showed a small peak for excluded proteins and a large, sharp peak for retarded proteins. When the urea proteins of all four tissue types were ultracentrifuged 100,000 x *g* for 2, 6, or 16 hr, gel and supernatant fractions were obtained. The amounts of urea protein obtained from normal epidermis by centrifugation and filtration were in good agreement. Similar results were observed with hyperplastic epidermis; however, the amount of protein in the excluded peak was less than that of normal epidermis. By gel filtration of papilloma and carcinoma urea proteins, 15-16% was found in the excluded peak, and 84-85% was found in the retarded protein peak. In contrast, centrifugation demonstrated nearly equal amounts of protein in the gel and supernatant fractions. Immunodiffusion of the fractions obtained by gel filtration and centrifugation in agar against antisera or IgG fractions of antisera, raised against the various urea proteins resulted in precipitin bands of identity, suggesting that the gel and supernatant fractions are closely related and differ only in their degree of polymerization. The results show that antigenic differences exist between the fibrous proteins of normal epidermis and papilloma or carcinoma, but the latter two tissues are antigenically similar with respect to these proteins.

4690 FIBROBLAST TUBULIN. (Eng.) Ostlund, R. (Natl. Cancer Inst., Bethesda, Md. 20014); Pastan*, I. *Biochemistry* 14(18):4064-4068; 1975.

Tubulin prepared from fibroblastic cells was characterized, and the content and properties of tubulin from normal and transformed cells were compared. Tubulin purified from L cells by Sepharose 4B and DEAE-cellulose chromatography had properties similar to brain tubulin. The specific activity of colchicine binding was 1.1 M of colchicine bound per 100,000 g of protein. Between 0.07 and 0.45% of the total protein of L cells was active tubulin. Proteins differing biochemically from tubulin but coelectrophoresing with it in sodium dodecyl sulfate gels were encountered. Colchicine-binding activity of virus transformed normal rat kidney (NRK) fibroblasts measured by a filter assay using a whole cell homogenate was reduced when compared to the parent NRK cells. L cells growing on plastic or glass surfaces had five times as much colchicine-binding activity as the same cells growing in spinner culture. Apparently, growth on a surface increases the tubulin content of L cells.

4691 THE HALF-LIFE OF POLYADENYLATED POLYSOMAL RNA FROM NORMAL AND TRANSFORMED CELLS IN MONOLAYER CULTURE. (Eng.) Sensky, T. E. (Faculty Medical Sciences, Univ. Coll. London, Gower St., London, WC1E 6BT, U.K.); Haines, M. E.; Rees, K. R. *Biochim. Biophys. Acta* 407(4):430-438; 1975.

RNA half-lives were estimated in five monolayer cell lines, including two pairs of normal cells and their transformed counterparts to ascertain whether alterations in control of gene expression involve changes in messenger (mRNA) stability. A line of transformed Chinese hamster kidney cells (transformed CHK) and their untransformed counterparts (CHK), CV-1 African Green Monkey kidney cells, BALB/c 3T3 mouse embryo fibroblasts, SV40-transformed 3T3 fibroblasts and a strain of 3T3 cells (XYT) were all labeled for at least two generations with 0.1 μCi/ml $^{32}P_i$. Medium, containing 0.1 μCi/ml $^{32}P_i$, 5 μCi/ml [^{3}H]uridine, and 5 μg/ml unlabeled uridine, was prepared in bulk so that labeling conditions would be uniform throughout the experiments. Experiments were started with the cells within two days after passage and continued for up to 40 hr. Cell growth was still exponential at the end of each experiment. The extracted polysomal RNA was fractionated on oligo(dT)-cellulose, the high and low salt fractions were precipitated with trichloroacetic acid, and acid-insoluble specific activity was determined as the $^3H/^{32}P$ ratio. The results for the polyadenylated fractions in all cases fit with those expected from a model in which the whole fraction has a single half-life of less than one generation time. From both the transformed/untransformed cell pairs, there was evidence that a relationship exists between cell generation time and the half-life of the polyadenylated polysomal RNA fraction; the relationship persists even through the process of transformation. It is concluded that considerable alteration in the pattern of RNA stability is unlikely to be obligatory in *in vitro* transformation.

4692 HEMOGLOBIN SYNTHESIS IN SOMATIC CELL HYBRIDS: GLOBIN GENE EXPRESSION IN HYBRIDS BETWEEN MOUSE ERYTHROLEUKEMIA AND HUMAN MARROW CELLS OR FIBROBLASTS. (Eng.) Deisseroth, A. (Natl. Heart Lung Inst., Bethesda, Md. 20014); Burk, R.; Picciano D.; Minna, J.; Anderson, W. F.; Nienhuis, A. *Proc. Natl. Acad. Sci. USA* 72(3):1102-1106; 1975.

Somatic cell hybrids were generated by fusion of mou Friend erythroleukemia cells either to mouse L cells (B82), human fibroblasts (W1-18 VA2), or human marro fractions enriched in erythroblasts. The hybrid cel were examined for globin gene expression by benzidin staining to detect cytoplasmic hemoglobin, and by molecular hybridization of cellular RNA to globin complementary DNA (cDNA) to detect globin messenger RNA (mRNA). The fibroblast (human or mouse) X erythroleukemia cell hybrids grown in monolayer retained most of the chromosomes of each parent. Neither cyt plasmic hemoglobin nor globin mRNA was detected in dimethylsulfoxide-treated fibroblast X erythroleukemia hybrid cells, indicating extinction of hemoglobi synthesis prior to the formation of cytoplasmic mRNA. The human marrow X mouse erytholeukemia hybrid cells grown in suspension culture contained only a few human chromosomes and exhibited low levels of hemoglobi synthesis which were amplified by 2% dimethylsulfoxi Mouse, but not human, globin mRNA was demonstrated i these hybrid cells. Expression of mouse hemoglobin synthesis in these hybrids may be due to the fact th they contained only a few human chromosomes and thus had lost any regulatory loci that may have prevented expression of hemoglobin synthesis in the fibroblast hybrids. The results suggest that somatic cell hybrids may be useful in searching for genetic factors which regulate activity of the globin genes.

4693 ASSEMBLY OF DNA AND PROTEIN DURING REPLICATION IN HeLa CELLS. (Eng.) Seale, R. L. (Natl. Inst. Arthritis, Metabl., Dig. Dis., Bethesda, Md.). *Nature* 255(5505):247-249; 1975.

The association of chromatin protein with DNA replication was investigated. Parallel digestion studies using pancreatic DNase I and staphylococcal nuclease were employed in probing the extent of DNA-protein associations. In studying the timing of addition of protein to chromatin, it was found that the least ^{3}H-thymidine-labeled DNA's were substantially more accessible to nuclease attack than control chromatin. The kinetics of maturation of nuclease resistance were qualitatively the same with both nucleases. Labeling experiments demonstrated that the progression of nuclease-susceptible nascent DNA to the relatively nuclease-resistant control chromatin represented a true precursor-product relationship. The period of 10-15 min observed for maturation of nuclease resistance was hence interpreted as representing chromatin protein addition, and corresponded with that for completion of replicons. In addition to the lag period noted, data indicated that DNA is replicated with pre-existant chromatin still attached, and that chromatin proteins protect DNA from nuclease digestion in a characteristic manner, unchanged by replicative processes. As the size

of nuclease-resistant DNA fragments was identical at all times, it was proposed that all chromatin yields the same size classes of resistant DNA fragments.

4694 NUCLEAR RIBONUCLEOPROTEIN COMPLEXES CONTAINING U1 AND U2 RNA. (Eng.) Raj, N. B. K. (Baylor Coll. Medicine, Houston, Tex. 77025); Ro-Choi, T. S.; Busch*, H. *Biochemistry* 14(20):4380-4385; 1975.

Nuclear ribonucleoprotein (RNP) complexes that contain the U1 and U2 RNA of chromatin of Novikoff hepatoma cells were extracted with 0.01 M Tris-HCl (pH 8.0) after the nuclei were initially washed with 0.075 M NaCl and 0.025 M EDTA (pH 8.0). These RNP complexes were purified by chromatography on Sepharose 6B columns and centrifugation on sucrose density gradients. The identity of the U1 and U2 RNA in these particles was established by their electrophoretic mobility in polyacrylamide gels and their T_1 RNase fingerprints, which were identical with those reported for authentic U1 and U2 RNA. The nuclear ribonucleoproteins had a buoyant density of 1.47 g/ml in CsCl gradients. Two-dimensional polyacrylamide gel electrophoresis of their proteins showed these RNP complexes contain ten polypeptide spots, of which two could be phosphorylated *in vivo*.

4695 ISOLATION OF A NUCLEAR RIBONUCLEOPROTEIN NETWORK THAT CONTAINS HETEROGENEOUS RNA AND IS BOUND TO THE NUCLEAR ENVELOPE. (Eng.) Faiferman, I. (Lindsley F. Kimball Res. Inst. of The New York Blood Center, New York, N.Y. 10021); Pogo*, A. O. *Biochemistry* 14(17):3808-3816; 1975.

Rapidly labeled polydispersed nuclear RNA from normal adult male rat liver and krebs ascites cells were demonstrated to be part of a ribonucleoprotein (RNP) network which in turn was tightly bound to the nuclear membrane. The membranous attachment, therefore, established a connection between chromatin and cytoplasm. The ultrastructure of the RNP network comprised fibrils and granules similar to those observed in intact nuclei. When bound to the nuclear membrane it had the composition of 63% protein, 14% RNA, 0.4% DNA, and 22.6% lipids. The proportion of lipids diminished to 2.2% when nuclear membrane was not present. Chromatin, nucleoli, and ribosomes were minor contaminants since histones and ribosomal proteins were not detectable by polyacrylamide gel electrophoresis. Nuclear disruption at high pressure in a French pressure cell caused fragmentation of the RNP network into a series of polydispersed RNP particles. Fragmentation could be prevented by using mild pressure, or by disrupting nuclei with high salt buffer and digesting the dispersed chromatin with deoxyribonuclease. A RNP network, almost free of membrane, was also obtained if the nucleus was deprived of its envelope by treatment with Triton X-100. Since no polydispersed RNP particles were found following dissolution of the nuclear membrane, it is assumed that the particles are componenets of the RNP network whose fragmentation occurs as a consequence of two processes: (a) activation of nuclear nucleases and (b) shearing forces.

4696 BIOCHEMICAL ESTIMATION OF THE BASIC DYE-BINDING CAPACITY OF RNA FROM RAT HEPATOMA. (Eng.) Lepage, R. (Institut du Cancer de Montreal, Montreal, Quebec, Canada); de Lamirande, G.; Daoust, R. *Cancer Res.* 35(1):45-48; 1975.

The RNA content of cell fractions was determined in normal male Sprague-Dawley rat liver and in solid Novikoff hepatoma to verify the possibility of an increased cytoplasmic RNA content in tumors. The possibility that cytoplasmic fractions of Novikoff hepatoma show greater affinity for basic dyes than corresponding normal fractions was examined by means of a test-tube toluidine blue-binding assay. The dye-binding capacity of total cytoplasmic fractions from tumors was 75% higher than normal after Carnoy fixation, which retains mostly ribosomal RNA. Assays on fresh ribosomes indicated that tumor ribosomes bound 71% more toluidine blue per milligram of RNA than the ribosomal preparation from normal liver. This study thus demonstrates a greater affinity of tumor RNA for basic dyes, and a comparison of biochemical and cytophotometric analyses suggests that an increase in basophilia by a factor of about 2 would be due to a qualitative alteration in ribosomal RNA molecules and/or ribosome structure in cancer cells.

4697 THE MESSENGER RNA SEQUENCES IN GROWING AND RESTING MOUSE FIBROBLASTS. (Eng.) Williams, J. G. (Dept. Biology, Massachusetts Inst. Technology, 77 Massachusetts Ave., Cambridge, Mass. 02139); Penman, S. *Cell* 6(2):197-206; 1975.

The sequences present in cytoplasmic messenger RNA (mRNA) in resting and growing cells of the mouse fibroblast line 3T6 were examined under controlled cellular proliferation by hybridization of complementary DNA (cDNA) to its RNA template. RNA was extracted at room temperature with phenol chloroform. The abundance and complexity classes of mRNA in growing 3T6 cells were compared to those in other established cell lines. The overall complexity measured for mRNA from HeLa cells and from mouse fibroblast lines 3T6, SV-PY-3T3, and L were quantitatively similar; they corresponded to approximately 10,000 and 8,400 sequences, respectively. The relative amount of the two major abundance classes and their complexities was identical in the three mouse fibroblast lines despite their different histories. HeLa cell mRNA was significantly different in the amount and complexity of the two major classes. Despite a reduced mRNA content, resting and growing 3T6 cells had a similar distribution with respect to its two mRNA complexity classes. Cross hybridization of cDNA and mRNA was employed to determine sequence homology between mRNA from resting and growing cell populations. The majority of mRNA sequences were the same in the two states. When the common se-

quences were removed, cross hybridization revealed that about 3% of the mRNA in resting cells was not present in the growing state; the opposite cross demonstrated that 3% of the mRNA in growing cells was not present in the resting cells. These differences may result from alterations in gene expression that are related to the growing state of the cell. The results suggest that mRNA populations of established lines of cultured mammalian cells resemble one another with respect to complexity and abundance classes. The similarity between the mouse fibroblast lines suggests either a stable pattern originating in the tissue or animal of origin, or a common selection pressure leading to quantitatively similar patterns of expression.

4698 RIBOSOMAL RNA METABOLISM IN SYNCHRONIZED PLASMACYTOMA CELLS. (Eng.) Eikhom, T. S. (Dep. Biochem., Univ. Bergen, Norway); Abraham, K. A.; Dowben, R. M. *Exp. Cell Res.* 91(2):301-309; 1975.

Ribosome synthesis and metabolism were studied in a mouse plasmacytoma cell line synchronized by isoleucine deprivation. Ribosomal RNA (rRNA) was characterized by gel electrophoresis. The rate of ribosome synthesis (as measured by the appearance of labeled rRNA in the cytoplasm) was low during the G1 phase, increased rapidly during the S phase, remained high during part of the G2 phase, and dropped to a minimum during mitosis. A slowdown in the increasing rate of RNA synthesis was observed during the middle of the S phase. No significant decrease in the total nucleotide pool per cell could be observed during the S phase. The accumulation of RNA (as determined by absorbance measurements) was highest during the S and G2 phases. Pulse labeling of rRNA and pulse chase experiments demonstrated that newly synthesized ribosomal subunits entered into free polysomes to the highest extent during the S phase. The percentage of membrane-bound polysomes of total polysomes increased during the G1 phase, as did the percentage of labeled rRNA in the membrane-bound fraction. The results suggest that newly synthesized ribosomal subunits enter into free or membrane-bound polysomes depending on the requirements of the cell. During the S phase they enter preferentially into free polysomes to produce mainly internal proteins; during the G1 phase they enter to a greater extent into membrane-bound polysomes, perhaps to produce more proteins destined for secretion.

4699 MEMBRANE-BOUND RIBOSOMES OF MYELOMA CELLS. II. KINETIC STUDIES ON THE ENTRY OF NEWLY MADE RIBOSOMAL SUBUNITS INTO THE FREE AND THE MEMBRANE-BOUND RIBOSOMAL PARTICLES. (Eng.) Mechler, B. (Dept. Biochemistry, Univ. Cambridge, England); Vassalli, P. *J. Cell Biol.* 67(1):16-24; 1975.

The kinetics of appearance of newly made 60S and 40S ribosomal subunits in the free and membrane-bound ribosomal particles of MOPC 21 (P3K) mouse myeloma cells were explored by determining the specific radioactivities of their 18S and 28S RN after various lengths of [^{3}H]uridine pulse. Bot 40S and 60S subunits entered free and membrane-bound polyribosomes at comparable rates from the cytoplasmic pool of newly made, free native subunits, the 40S subunits entering the native subunit pool and the polyribosomes slightly earlier than the 60S subunits. At all times, the specif radioactivity of the membrane-bound native 60S subunits was slightly lower than that of the ribosomal 60S subunits. This indicates that the membrane-bound native 60S subunits are not precurso destined to enter membrane-bound polyribosomes a suggests that they result from the dissociation ribosomes after chain termination. The results also suggest that the membrane-bound native 60S subunits are not reutilized before their release from the membranes, which probably takes place shortly after dissociation from their 40S subuni The monoribosomes, both free and membrane-bound, had the lowest specific radioactivities in their subunits. Finally, a small amount of newly made native 40S subunits, containing 18S RNA of high specific radioactivity, and apparently also newl made messenger RNA were detected on the membrane The high turnover of these membrane-bound native 40S subunits suggests that they may represent initiation complexes formed with mRNA which has just reached the membranes and which has not yet given rise to polyribosomes.

4700 ASSOCIATION OF THE POLYADENYLATE SEGMENT OF MESSENGER RNA WITH OTHER POLYNUCLEOTIDE SEQUENCES IN MOUSE SARCOMA 180 POLYRIB SOMES. (Eng.) Jeffery, W. R. (Tufts Univ. Sch. Med., Boston, Mass.); Brawerman, G. *Biochemistry* 14(15):3445-3451; 1975.

The isolation from mouse sarcoma 180 ascites cell of a structure consisting of poly(A) in associati with other polyribonucleotide sequences is report Polysomes and polysomal RNA from mouse sarcoma 18 cells were hydrolyzed with 1 μg/ml of pancreatic ribonuclease (RNase), and the digested RNA fragments containing poly(A) sequences were selected by adsorption on Millipore filters and purified by oligo(dT)-cellulose chromatography. The RNA fragments were also subjected to polyacrylamide gel electrophoresis, and their interaction with poly(U) was studied. Some of the RNA fragments bound to the Millipore filters contained pyrimidine nucleotides as well as poly(A), and at lea a portion of the poly(A) segment in these fragmen was available for complementary base pairing with poly(U). Heating or formamide treatment caused the dissociation of poly(A)-free fragments from the poly(A)-containing fragments. The two types of fragments tended toward reassociation under annealing conditions, this association being prevented by poly(U). Various control experiments indicated that the poly(A)-containing structure was not an artifact generated during manipulation of the polysomes, the same structure being obtainable by limited RNase digestion of polyribosomes, followed by deproteinization. The results suggest

that the messenger RNA in polyribosomes may have a defined configuration causing the interaction of the poly(A) sequence with another RNA segment.

4701 EFFECTS OF ESTRADIOL ON UTERINE RIBONUCLEIC ACID METABOLISM. ASSESSMENT OF TRANSFER RIBONUCLEIC ACID METHYLATION. (Eng.) Munns, T. W. (St. Louis Univ. Sch. Medicine, St. Louis, Mo. 63104); Sims, H. F.; Katzman, P. A. *Biochemistry* 14(21):4758-4764; 1975.

The methylation of uterine transfer RNA (tRNA) was assessed in immature female rats (21-22 days old) following estrogen treatment by examining the *in vitro* tRNA methyltransferase activity and by characterizing the types and amounts of methylated constituents that appeared on newly synthesized uterine tRNA. The rats were injected ip with a single dose of 10 μg of 17β-estradiol in 0.25 ml aqueous 0.5% ethanol. The rats were sacrificed 1-24 hr later. Groups of 6-12 uteri were labeled by one of three systems to assess the methylation of tRNA: (1) a 90-min pulse with [*methyl*-^{14}C]methionine (11.2 μCi/incubation) followed by a 60-min chase in the presence of unlabeled methionine, (2) a 120-min pulse with [U-^{14}C]guanosine (10.2 μCi/incubation) in the presence of unlabeled adenosine (5×10^{-6} M) and methionine (3.3×10^{-5} M) followed by a 60-min chase with actinomycin D (20 μg/uterus), and (3) a 90-min pulse with [*methyl*-^{3}H]methionine (500 μCi/incubation) in the presence of actinomycin D (20 μg/uterus) followed by a 60-min chase with unlabeled methionine. Methylase activity was obtained by measuring the incorporation rate of methyl groups from S-adenosyl[*methyl*-^{14}C]methionine into heterologous tRNA (*Escherichia coli* B) in the presence of uterine cytosol preparations (100,000 x *g* supernatants). Total RNA was extracted from uterine homogenates with phenol-sodium dodecyl sulfate; tRNA was separated by salt fractionation. Immature rats treated with estradiol demonstrated both increased methylation of uterine tRNA and increased methylase activities largely attributable to an increased tRNA synthesis rate rather than gross changes in either the type or amount of methylated constituents. Estrogen treatment failed to significantly alter the following: (1) resulting patterns of *methyl*-^{14}C-methylated constituents of tRNA, (2) the extent to which [2-^{14}C]adenine residues incorporated into tRNA become methylated, (3) the extent of methylation of precursor tRNA in the absence of tRNA synthesis, and (4) the types of methylase activities expressed *in vitro*. In addition, these results have demonstrated an enhanced tRNA synthesis followed by increased synthesis and accumulation of uterine protein.

4702 DIFFERENTIATION OF ERYTHROLEUKEMIC CELLS IN THE PRESENCE OF INHIBITORS OF DNA SYNTHESIS. (Eng.) Leder, A. (Natl. Inst. Child Health and Human Development, Bethesda, Md. 20014); Orkin, S.; Leder, P. *Science* 190(4217):893-894; 1975.

The ability of erythroleukemic mouse T3C12 cells to undergo erythroid differentiation in the presence of butyric acid and inhibitors of DNA synthesis was determined by assaying cells for the percent of benzidine-positive (Hb-containing cells). At 1 mM, butyric acid readily induced erythroid differentiation in both log phase and stationary phase cells. Cytosine arabinoside (1 μg/ml) and hydroxyurea (0.1 mM) quickly inhibited both DNA synthesis and cell division in butyric acid-treated cells but had no effect on cell differentiation. These results appear to rule out more complex models for globin gene expression which require gene replication or cell division (or both).

4703 DEMONSTRATION THAT A MOUSE IMMUNOGLOBULIN LIGHT CHAIN MESSENGER RNA HYBRIDIZES EXCLUSIVELY WITH UNIQUE DNA. (Eng.) Rabbitts, T.H. (Medical Res. Council, Lab. Molecular Biology, Hills Road, Cambridge CB2 2QH, England); Jarvis, J. M.; Milstein, C. *Cell* 6(1):5-12; 1975.

^{32}P-labeled light chain messenger RNA was prepared from mouse MOPC 21 myeloma cells. The messenger RNA was hybridized to purifed repetitive nuclear DNA and both the hybridized (repetitive ^{32}P-RNA) and nonhybridized (nonrepetitive ^{32}P-RNA) fractions were isolated. A T1 ribonuclease fingerprint was given only by the nonhybridized RNA which showed that oligonucleotides derived from the variable and constant regions of the light chain messenger RNA. The fingerprint also showed that oligonucleotides were derived from the untranslated regions of the light chain messenger RNA. The nonrepetitive ^{32}P-RNA rehybridized only with the unique fraction of total nuclear DNA. The rapidly hybridizing part of the unfractionated ^{32}P-RNA preparation, therefore, is not a component of the light chain messenger RNA itself. Complementary DNA was prepared with reverse transcriptase using unlabeled light chain messenger RNA as template, and the transcripts were fractionated into various size classes. Complementary DNA molecules greater than 900 bases in length hybridized with both the initial messenger RNA and with the nonrepetitive ^{32}P-RNA but failed by hybridize with excess purified repetitive ^{32}P-RNA. The rapidly hybridizing component of the messenger RNA fraction, therefore, does not appear to be transcribed by reverse transcriptase. It is concluded that, under the experimental conditions used, the light chain messenger RNA hybridizes exclusively with unique DNA.

4704 CHARACTERIZATION OF NOVIKOFF HEPATOMA mRNA METHYLATION AND HETEROGENEITY IN THE METHYLATED 5' TERMINUS. (Eng.) Desrosiers, R. C. (Dept. Molecular Biophysics and Biochemistry, Yale Univ., New Haven, Conn. 06520); Friderici, K. H.; Rottman, F. M. *Biochemistry* 14(20):4367-4374; 1975.

KOH digestion of methyl-labeled poly(A)$^{+}$ Novikoff hepatoma messenger RNA (mRNA) purified by (dT)-cellulose chromatography produced mononucleotide and multiple peaks of a large oligonucleotide (-6 to -8 charge) when separated on the basis of charge by Pellionex-WAX high-speed liquid chroma-

tography in 7 M urea. Heat denaturation of the RNA before application to (dT)-cellulose was required to release contaminants (mostly 18S ribosomal RNA) that persisted even after repeated binding to (dT)-cellulose at room temperature. Analysis of the purified poly(A)$^+$ mRNA by enzyme digestion, acid hydrolysis, and a variety of chromatographic techniques demonstrated that the mononucleotide (53%) was due entirely to N^6-methyladenosine. The large oligonucleotides (47%) were found to contain 7-methylguanosine and the 2'-O-methyl derivatives of all four nucleosides. No radioactivity was found associated with the poly(A) segment. Periodate oxidation of the mRNA followed by β elimination released only labeled 7-methylguanine consistent with a blocked 5' terminus containing an unusual 5'-5' bond. Alkaline phosphatase treatment of intact mRNA had no effect on the migration of the KOH produced oligonucleotides on Pellionex-WAX. When RNA from which 7-methylguanine was removed by β elimination was used for the phosphatase treatment, distinct dinucleotides (NmpNp) and trinucleotides (NmpNmpNp) occurred after KOH hydrolysis and Pellionex-WAX chromatography. Thus, Novikoff hepatoma poly(A)$^+$ mRNA molecules can contain either one or two 2'-O-methylnucleotides linked by a 5'-5' bond to a terminal 7-methylguanosine, and the 2'-O-methylation can occur with any of the four nucleotides. The 5' terminus may be represented by $m^7G^{5'}ppp^{5'}$ $(Nmp)_{tor2}Np$, a general structure proposed earlier as a possible 5' terminus for all eucaryotic mRNA molecules. The composition analyses indicated that there are three N^6-methyladenosine residues, one 7-methylguanosine residue, and 1.7 2'-O-methylnucleoside residues per average mRNA molecule.

4705 TRANSCRIPTION OF MOUSE DNA. (Eng.) Ivanov, I. G. (Inst. Biochemistry, Bulgarian Acad. Sciences, Sofia 13, Bulgaria); Zlateva, B. S.; Markov, G. G. *Dokl. Bolg. Akad. Nauk* 28(6): 813-816; 1975.

The transcription of the three basic families of mouse DNA (highly repeated, intermediate, and unique) was studied. DNA was isolated from mouse liver and Ehrlich ascites tumor cells (EAT), and [^{3}H]-DNA was obtained from EAT cells by injecting the animals with [^{3}H]thymidine on the seventh day after transplantation. Labeled and unlabeled pre-mRNA (HnRNA) was isolated from mouse liver and EAT, and hybridization experiments were performed in solution and on membrane filters. Saturation of highly repeated and intermediate DNA with the 63 C fraction of heterogeneous nuclear RNA (63-RNA) was reached at RNA concentrations of 25-50 μg/ml. With 85-RNA, the saturation curves of the same DNAs tended toward a biphasic character. Both heterogeneous RNA fractions hybridized with the total DNA to about the same degree (6%), although the intermediate DNA had a greater ability to hybridize with 63- and 85-RNA. Under the conditions used for the isolation of highly repeated DNA, the renaturation of satellite DNA was completed. Under these conditions, about 15% of the DNA behaved as highly repeated, and it was transcribed to a considerable extent in 63- and 85-RNA. EAT-DNA was a good substitute for mouse DNA, both having identical properties with respect to reassociation and hybridiz tion. It is concluded that highly repeated DNA sequences participate to a large extent in the formation of the primary transcriptional products of the operons.

4706 DNA SYNTHESIS IN ISOLATED HeLa CELL NUCLEI. OPTIMALIZATION OF THE SYSTEM AND CHARACTERIZATION OF THE PRODUCT. (Eng.) Krokan, H. (Inst. Medical Biology, Univ. Tromso, 9000 Tromso, Norway); Bjorklid, E.; Prydz*, H. *Biochemistry* 14(19):4227-4232; 1975.

DNA replication in isolated nuclei from synchroniz HeLa S_3 cells was studied in an effort to optimali the system and characterize the product. The synthesis was dependent on deoxy-GTP, deoxy-CTP, deox ATP, ATP, and Mg^{2+}. Optimum pH was 7.8. NH_4Cl pl Tris-HCl (each 65 mM) plus glycerol further stimulated the system. The four ribonucleoside triphosphates gave a slight, reproducible and additive stimulation. Low concentrations of spermine and spermidine (0.2-1.5 x 10^{-4} M) were also stimulator (10-15%) whereas higher concentrations were inhibitory. The reaction product was DNase-sensitive, a banded at 1.699 g/ml in neutral CsCl together with bulk HeLa nuclear DNA. 85% of the [^{3}H]thymidine triphosphate incorporated banded at densities abov normal, suggesting *in vitro* elongation of strands already initiated *in vivo*.

4707 NUCLEAR DNA OF MOUSE HEPATOMA STUDIED BY ^{3}H-ACTINOMYCIN D BINDING. (Eng.) Aczel, J. (Dept. Biol. Sci., Sir George Williams Univ., 1455 de Maisonneuve Blvd. West, Montreal, Quebec, H3G 1M8, Canada); Enesco, H. E. *Experientia* 31(2): 229-230; 1975.

The distribution of DNA in normal liver and hepatom cell nuclei was compared with special reference to heterochromatin in hepatoma-bearing mice (Jax code BW 7756) and normal C57L/J mice. Three experimenta methods were used which differed in the sequence of fixation (gluteraldehyde and osmium tetroxide) and ^{3}H-actinomycin D incubation. Slides were stained i 1% toluidine blue. Silver grains, representing ^{3}H-actinomycin D-DNA binding sites, were counted over 10 randomly selected nuclei for each of nine hepatomas and nine liver preparations. The liver paren chyma nuclei were classed as diploid or tetraploid on the basis of nuclear diameter measurements made with a calibrated ocular micrometer. The area of t tetraploid liver cell nuclei (49.94 μm^2) was nearly twice that of the diploid nuclei (28.56 μm^2), while the hepatoma cell nuclei were much larger than eith (115.47 μm^2). Proof that ^{3}H-actinomycin D binds sp ifically to DNA was provided by the grain count dat obtained from the enzyme treated control sections. RNA extraction did not influence ^{3}H-actinomycin D binding, but when the DNA was extracted, no binding occurred. The grain density over diploid and tetraploid liver cell nuclei was almost identical in all

experiments (93 grains/100 μm^2) showing that DNA dis-
:ribution was not altered by the increase in ploidy.
In marked contrast, the ^{3}H-actinomycin D binding to
nepatoma cell nuclei (200 grains/100 μm^2) was more
:han twice as dense as in the normal liver cells.

708 HUMAN LEUKEMIC INTERMEDIATE DNA COMPONENTS. (Eng.) Corneo, G. (Centro di Patologica Molecolare, Via Pace 15, I-20122 Milano, Italy); Sinelli, E.; Polli, E. *Acta Haematol. (Basel)* 54(4): 210-220; 1975.

The DNA extracted from human leukemic WBC was fraction on a methylated albumin kieselguhr (MAK) column. The different fractions obtained were reannealed to a Cot value of 20 M x sec/l to study the distribution of the intermediate DNA on the MAK column. Intermediate DNA was found to contain two components: One (CsCl density after reannealing, 1.703 g/ml) was obtained by reannealing high molecular weight DNA, and the other (CsCl density after reannealing, 1.707 g/ml) was obtained only by reannealing sonicated low molecular weight DNA. High molecular weight intermediate DNA (1.703 component) eluted early from the MAK column in the fractions corresponding to the main DNA peak. Low molecular weight intermediate DNA (1.707 component) was more widespread on the MAK column, but appeared to be enriched in the fractions eluted later. The possibility is discussed that the latter component is interspersed in that part of the genome which is apparently more homogeneous in density in an analytical CsCl gradient, and is absent on the skewed, more heterogeneous, heavy side of the main DNA in CsCl.

09 ABNORMAL RESPONSE OF GLYCOLIPID SYNTHESIS TO TEMPERATURE IN TRANSFORMED BHK CELLS THERMOSENSITIVE FOR GROWTH CONTROL. (Eng.) Buehler, (Boston Univ. Sch. Medicine, Boston, Mass. 02118); Moolten, F. *Biochem. Biophys. Res. Commun.* 63(1):91-96; 1975.

Glycolipid synthesis was studied in dimethylnitrosamine-transformed BHK cell line DMN4B. (This line exhibits transformed behavior at 38.5 C but not at 39 C). The cultures were incubated with 0.7 µCi-[^{14}C]palmitate, and the glycolipids were isolated by two-dimensional thin layer chromatography, detected by autoradiography and quantified by liquid scintillation spectrometry. [^{14}C]-palmitate incorporation into mono-, di-, and trihexosylceramides was unimpaired at 32 C when compared with incorporation rates in untransformed BHK cells incubated at the same temperature. At 38.5 C, labeling of these glycolipids increased greatly in the BHK cells, but failed to increase comparably in the DMN4B cells. Assay of cell-free preparations of alpha-galactosyltransferase, which catalyzes trihexosylceramide synthesis, revealed a stimulatory effect of increased temperature on activity of the BHK enzyme, but not the DMN4B enzyme. The results suggest that transformation can result from a mutation affecting glycolipid synthesis.

4710 THE SYNTHESIS OF FORSSMAN GLYCOLIPID IN CLONES OF NIL 2 HAMSTER FIBROBLASTS GROWN IN MONOLAYER OR SPINNER CULTURE. (Eng.) Sakiyama, H. (Div. Physiology and Pathology, Natl. Inst. Radiological Sciences, 9-1, 4 chome, Anagawa Chiba-shi 280, Japan); Terasima, T. *Cancer Res.* 35(7):1723-1726; 1975.

The amount of Forssman glycolipid (GL-5) was investigated in two clones of Nil hamster cells grown either in monolayer or in spinner culture. GL-5 assayed by the complement-fixation inhibition test increased with increasing cell density in the monolayer. However, cells grown in spinner cultures failed to show the density-dependent response in both clones examined. Cells transformed by hamster sarcoma virus did not show the density-dependent increase of GL-5, even when grown in monolayer. The effect of transfer from confluent to sparse cultures on the amount and the synthesis of GL-5 was also examined. The amount of GL-5 did not change significantly before the first cell division and then decreased until the third day after transfer; in contrast, the synthesis of GL-5 dropped markedly before the first cell division and continued to decrease until three days after transfer. It is suggested that the presence of a high level of density-sensitive glycolipid does not by itself inhibit cell division and that intercellular contact is probably not the sole factor responsible for activation of GL-5 synthesis.

4711 ACYLTRANSFERASES AND THE BIOSYNTHESIS OF PULMONARY SURFACTANT LIPID IN ADENOMA ALVEOLAR TYPE II CELLS. (Eng.) Snyder, F. (Medical and Health Sciences Div., Oak Ridge Associated Univ., Oak Ridge, Tenn. 37830); Malone, B. *Biochem. Biophys. Res. Commun.* 66(3):914-919; 1975.

Alveolar type II adenoma cells were used to investigate the nature of the acyltransferases associated with the endoplasmic reticulum. The adenomas were harvested from the lungs of female BALB/c mice that had been injected ip with urethan (1 mg/g for three consecutive days) approximately six months earlier. Acyltransferase activities were determined in a system containing an acyl acceptor, adenoma microsomes (0.8 mg protein), CoA (200 µM), ATP (10 mM), Mg^{2+} (4 mM), and [1-^{14}C]palmitic acid (33.3 µM). All samples were incubated for 20 min at 37 C. The microsomal preparations were found to contain acyltransferases that transferred palmitate to *rac*-glycerol-3-P to form phosphatidic acid, to dihydroxyacetone-P to form acyldihydroxyacetone-P, and to 1-acyl-*sn*-glycero-3-phosphocholine to form 3-*sn*-phosphatidylcholine. The data demonstrate that the microsomal preparations can catalyze significant incorporation of palmitic acid into the 2-position of the disaturated species of 3-sn-phosphatidylcholine independently of phosphatidic acid formation as evidenced by the fact that *sn*-glycerol-3-P and Ca^{2+} (which inhibits choline phorphotransferase) did not influence the incorporation of palmitic acid into the main surfactant lipid. Thus, a deacylation-acylation reaction involving 2-lysophosphatidylcholine appears to be an important pathway

for the synthesis of surfactant lipid in alveolar type II cells; the control of acyl specificity at the 2-position is determined by the relative concentrations of the coparticipating substrates, 1-palmitoyl-*sn*-glycero-3-phosphocholine and palmitoyl-CoA.

4712 MARKED REDUCTION OF CYCLIC GMP PHOSPHODIESTERASE ACTIVITY IN VIRALLY TRANSFORMED MOUSE FIBROBLASTS. (Eng.) Lynch, T. J. (St. Jude Children's Res. Hosp., Memphis, Tenn. 38101); Tallant, E. A.; Cheung, W. Y. *Biochem. Biophys. Res. Commun.* 65(3):1115-1122; 1975.

Cyclic AMP phosphodiesterase and cyclic GMP phosphodiesterase activities were determined in normal 3T3 and transformed mouse fibroblasts and the effect of dibutyryl cyclic AMP on these enzymes was investigated. Normal mouse fibroblasts and fibroblasts transformed by simian virus 40 were plated in culture dishes to a final density of 150,000-400,000 cells/plate in modified Eagle's medium and harvested before confluency. In some cultures, the medium was changed 48 hr after plating and replaced with medium containing 1 mM dibutyryl cyclic AMP, 1 mM theophylline, and sometimes actinomycin D (1 μg/ml). The cells were incubated for an additional ten hours before being harvested and assayed. Phosphodiesterase was assayed with radioactive cyclic AMP or cyclic GMP using an anionic exchange resin. In the normal cells, the specific activities of cyclic AMP phosphodiesterase and cyclic GMP phosphodiesterase were 62 and 41, respectively; in the transformed cells, the two activities were 47 and 4, respectively. In the transformed fibroblasts, therefore, both enzyme activities were significantly lower but the reduction was much more pronounced with cyclic GMP phosphodiesterase. Incubation with dibutyryl cyclic AMP increased both cyclic AMP and cyclic GMP phosphodiesterase activities, but the increase was larger with cyclic AMP than with cyclic GMP phosphodiesterase. The elevation of both activities was blocked by actinomycin D, indicating that the increase of enzyme activity involved the synthesis of new messenger RNA. The differential increase in cyclic AMP phosphodiesterase by dibutyryl cyclic AMP and the disparate reduction in cyclic GMP phosphodiesterase in the transformed fibroblasts suggest that the two enzymes are regulated separately.

4713 PURIFICATION OF ARGINASES FROM HUMAN-LEUKEMIC LYMPHOCYTES AND GRANULOCYTES: STUDY OF THEIR PHYSICOCHEMICAL AND KINETIC PROPERTIES. (Eng.) Reyero, C. (Institut fur Biochemie, Tierarztliche Hochschule, Linke Bahngasse 11, A-1030 Wien, Austria); Dorner, F. *Eur. J. Biochem.* 56(1): 137-147; 1975.

Because purification studies on normal human WBC is impeded by lack of sufficient starting material, the possible chemical differences of the arginases of leukemic lymphocytes and leukemic granulocytes were investigated. Arginase was isolated from granulocytes of a patient with chronic myelocytic leukemia and from lymphocytes of a patient with chronic lymphocytic leukemia. Both enzymes were purified to apparent homogeneity. The purification procedure involved acetone extraction, ammonium sulfate precipitation, DEAE-cellulose and CM-Sephadex chromatography, and gel filtration on Bio-Gel A 1.5 m. Both enzymes appeared to be metalloenzymes, and to have molecular weights of about 120,000. Studies with the dissociated enzyme suggested that the subunit molecular weight is abou 37,000, in agreement with a tetrameric aggregate structure of the native enzymes. Human leukemic granulocyte and lymphocyte arginases were found to be strongly basic proteins with p*I* values between 9.25 and 9.35. Their free -SH groups enabled them to be linked to organomercurial-agarose. The kinetic properties estimated for both enzymes showed an optimum pH of 8.5, and an optimal $MnCl_2$ concentration of 0.01 M. The K_m for L-arginine was 2.7-3.1 mM, and L-ornithine exhibited a mixed type of inhibition, with a K_i of 15.5-15.7 mM. The two enzymes described are similar to one another and differ only slightly in properties from the previously well-characterized rat liver enzyme.

4714 MECHANISMS OF LYSOSOMAL ENZYME RELEASE FROM HUMAN POLYMORPHONUCLEAR LEUKOCYTES: EFFECTS OF PHORBOL MYRISTATE ACETATE. (Eng.) Goldstein, I. M. (New York Univ. Sch. Medicine, New York, N.Y. 10016); Hoffstein, S. T.; Weissmann, G. *J. Cell Biol.* 66(3):647-652; 1975.

Since the secretion of blood polymorphonuclear leukocyte (PMN) lysosomal enzymes by translocation of cell granules to the cell periphery and the fusion of the granule membrane with the plasma membrane is promoted by cyclic 3',5'-guanosine monophosphate (cGMP), and since phorbol myristate acetate (PMA), a potent tumor-promoter, raises the level of cGMP in various cell types, it was of interest to determine the possible direct effect of PMA upon lysosomal enzyme release. Leukocytes were prepared from human donors by sedimentation in dextran and lysis of RBC. After preincubation of 2-4 x 10^6 leukocytes with cytochalasin B (5 μg/ml) for 10 min at 37 C, followed by incubation with either zymosan (0.5 mg/ml) for 15 min or complement component C5a for 5 min, the reaction mixtures were assayed for beta-glucuronidase, lysozyme, and lactic dehydrogenase (LDH). The effect of PMA was determined by adding 20 ng/ml of the substance after the preincubation with cytochalasin B. Significant enhancement (36.8%) of beta-glucuronidase release was observed if PMA was added 1 min before the zymosan, but maximal enhancement (62.1%) occurred when the two were added simultaneously. The increment in beta-glucuronidase was not accompanied by an increment in LDH release. Similar results were obtained using C5a instead of zymosan. In the absence of either zymosan or C5a, beta-glucuronidase was not released in significant amounts from cytochalasin B-treated PMN's exposed to PMA. Lysozyme, however, was released from these cells. In human PMN's, lysosome-containing granules thus appear to be distinct from the azurophilic granules which secrete beta-glucuronidase. Electron micrographs of cells exposed to PMA revealed an increase in the

number of visible cytoplasmic microtubules as compared to control cells. Enhancement of beta-glucuronidase release by PMA appeared to be independent of effects of the PMA on release of lysozyme and is likely due to PMA-induced elevations of cellular cGMP.

4715 LEUKOPOIESIS AND ALKALINE PHOSPHATASE OF LEUKOCYTES IN ECHINACIN TEST IN ULCERATIVE COLITIS. (Ger.) Djonlagic, H. (II. Med. Klinik und Poliklinik der Med. Hochschule Lubeck, D-24 Lubeck, Ratzeburger Allee 160, West Germany); Feiereis, H. *Z. Gastroenterol.* 13(1):19-22; 1975.

The leukocyte count, leukocyte distribution, and leukocyte alkaline phosphatase activity were studied in ten patients (five men, five women) with untreated recurrent ulcerative colitis and in ten normal control subjects 1, 2, 3, 5, 8, 11, and 24 hr after iv injection of 1-1.5 ml of echinacin. The increase in the number of neutrophils with bacilliform nuclei in the peripheral blood was about the same in the two groups, while the number of leukocytes with segmented nuclei was slightly lower in the patients than in the control. The leukocyte alkaline phosphatase activity was generally higher in the patients in whom the initial level had been higher than in the control. It is not known whether the increased alkaline phosphatase activity in ulcerative colitis is due to the primary inflammatory process or to secondary infections. The findings indicate that the leukocyte alkaline phosphatase is a more sensitive indicator of the primary and secondary inflammatory process than the degree of the increase in the leukocyte count.

4716 DNA-DEPENDENT RNA POLYMERASES OF EHRLICH CARCINOMA, OTHER MURINE ASCITES TUMORS, AND MURINE NORMAL TISSUES. (Eng.) Blair, D. G. R. (Dept. Cancer Res., Univ. Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0). *J. Natl. Cancer Inst.* 55(2):397-412; 1975.

The separation and characterization of Ehrlich ascites carcinoma (EAC) DNA-dependent RNA polymerases are described. The enzyme was solubilized from the nuclei of EAC cells by sonic disruption in the presence of 0.3 M $(NH_4)_2SO_4$, and the multiple RNA polymerases were separated by chromatography on DEAE-Sephadex A-25. Elution with a one-step gradient of $(NH_4)_2SO_4$ yielded five peaks of activity which were designated RNA polymerases 1a, 1b, 11a, 11b, and 111; 11b was the most prominent. Linear-gradient elution also yielded five peaks of the same designation, but 1a and 1b, as well as 11a and 11b, were not well separated. 11a and 11b were completely inhibited by α-amanitin (0.1 μg/ml) whereas the other forms were not. EAC RNA polymerases 1a, 1b, 11a, and 11b assessed Mg^{2+}, Mn^{2+}, and $(NH_4)_2SO_4$ optima, molecular weights, and thermal sensitivities similar to those reported for other mammalian DNA-dependent RNA polymerases. As measured by relative ribonucleoside monophosphate incorporation with native calf thymus DNA template, EAC RNA polymerases 1a and 1b synthesized ribosomal RNA-like products, whereas forms 11a, 11b, and the parent enzyme mixture synthesized compounds that were more similar to DNA. No species specificity was found for DNA templates, and denatured DNA was consistently preferred to the native template by 11a and 11b; the two kinds of template were about equally efficient for forms 1a and 1b. Although forms 1a, 11b, and 11a were all inhibited by daunomycin (5.0, 10.0, and 20.0 μg/ml), form 11a was preferentially affected. 3',5'-Cyclic (2×10^{-6} M), 3',5'-cyclic guanosine monophosphate (2×10^{-6} M) and gibberellic acid (2.8 - 277 μg/ml) implicated as RNA polymerase regulators in other systems, were generally ineffective. The levels of nuclear RNA polymerase activity, per milligram of DNA, in three mouse ascites tumors (EAC, 6C3HED lymphosarcoma, and TA3 adenocarcinoma) were compared with those from three normal mouse tissues (kidney, liver, and spleen). On the average, the tumor nuclei contained 8.9, 1.5, 2.7, 20.0, and 3.8 times the activities of RNA polymerases 1a, 1b, 11a, 11b, and 111, respectively, as the normal cells, but the difference was significant only for 11b.

4717 CHARACTERIZATION OF TERMINAL DEOXYNUCLEOTIDYLTRANSFERASE IN A CELL LINE (8402) DERIVED FROM A PATIENT WITH ACUTE LYMPHOBLASTIC LEUKEMIA. (Eng.) Sarin, P. S. (Natl. Cancer Inst., NIH, Bethesda, Md.); Gallo, R. C. *Biochem. Biophys. Res. Commun.* 65(2):673-682; 1975.

Terminal deoxynucleotidyltransferase in a cell line (8402) derived from the blood cells of a patient with acute lymphoblastic leukemia was characterized. The activity is comparable to the levels present in thymus gland. The terminal transferase from these cells was purified by successive chromatography on DEAE cellulose, phosphocellulose, and hydroxyapaptite columns to approximately 900-fold. The purified enzyme had a sedimentation value of 3.4S, a pH optimum of 7.8, a Mn^{2+} optimum of 0.1 mM, and a Mg^{2+} optimum of 7 mM. The purified enzyme efficiently utilized a number of oligo or poly deoxynucleotide initiators and was similar in its properties to the terminal deoxynucleotidyltransferase purified from calf thymus and from the blast cells of some patients with chronic myelogenous leukemia.

4718 ISOLATION AND SOME PROPERTIES OF EXORIBONUCLEASE FROM RAT LIVER CELL NUCLEI. (Rus.) Skridonenko, A. D. (Res. Inst. Health Resort Sci., Odessa, USSR). *Biokhimiia* 40(1):13-20; 1975.

Exoribonuclease was first obtained and purified from Ehrlich's mouse ascites cell nuclei, mouse liver cells and other tissues and its properties were described in the late 60's. Working on the ribonuclease action of rat liver cell nuclei, the author succeeded in isolating and purifying an exoribonuclease analogous to that of Ehrlich's ascites cells. Lazarus and Sporn's method for the isolation of rat liver cell nuclei and determination of exoribonuclease activity was used. The enzyme was obtained by extraction from a rat liver homogenate, first at

pH 6.0, then at pH 8.0, followed by a dual fractionation with ammonium sulfate. Further purification was attained by columnar chromatography (DEAE-Sephadex A-50). Its maximal activity was reached at pH 7.4-7.6 in an acid buffer (tris-HCl, tris-acetate). In order to be optimally effective, the presence of Mg ions was required. Chromatographic data showed that exoribonuclease was essentially localized in the chromatin of the cell nucleus (80-90%), the balance (10-20%) in acid and residual proteins. The investigations indicated that the ribonuclease split synthetic polynucleotides and RNA forming ribonucleoside-5'-phosphates. The enzyme preferably reacted with single-stranded polyribonucleotides and required much more time to hydrolyze multi-chain-containing helical structures. The author concluded that the enzyme studied broke down the "non-informative" (unstable, fast disintegrating within the nucleus) portion of the newly formed high-polymer cellular RNA which, however, remains to be corroborated.

4719 THE STEROID ALCOHOL AND ESTROGEN SULFOTRANSFERASES IN RODENT AND HUMAN MAMMARY TUMORS. (Eng.) Godefroi, V. C. (Michigan Cancer Foundation, Detroit, Mich. 48201); Locke, E. R.; Singh, D. V.; Brooks, S. C. *Cancer Res.* 35(7): 1791-1798; 1975.

Rodent and human mammary tumor systems were investigated to relate the steroid alcohol and estrogen sulfotransferase activities to the hormonal dependency of the tumor as determined by estrogen receptor content. Unlike the normal mammary gland or the hyperplastic alveolar nodule, rodent mammary neoplasms displayed significant levels of these two sulfotransferases. In the hormone-independent mouse tumors produced from outgrowth lines D_1, D_2, and D_8, high dehydroepiandrosterone sulfotransferase activity was characteristic of the rapidity with which hyperplastic alveolar nodules developed into a neoplasm (V_{max} = 52.8 vs 1.8 fM/min/mg protein) while estrone sulfotransferase activity was either not detectable or low (V_{max} = 5.5 fM). After oophorectomy of BALB/c mice bearing slowly developing tumors, both sulfotransferases in the nonregressing neoplasms showed marked increases in activity (V_{max} dehydroepiandrosterone = 30.0 fM; V_{max} estrone = 18.5 fM). Strain differences were found to influence the steroid-sulfating capability but not the estrogen receptor content of hormone-dependent rat mammary tumors. In Wistar-Lewis rats the steroid alcohol sulfotransferase activity was at least 35 times higher than in the Sprague-Dawley strain. As was observed in the mouse mammary tumor, Sprague-Dawley rat neoplasms that grew in the absence of ovarian hormones contained significantly greater levels of the steroid alcohol sulfotransferase. A possible correlation between presence of the steroid alcohol sulfotransferase and the estrogen receptor protein was observed in a limited number of human breast carcinomas. A positive clinical response of four patients to hormonal manipulation was matched in all four cases with the presence of estrogen receptor protein and in three with the presence of the steroid alcohol sulfotransferase. The data support the concept that the sulfotransferase pattern of breast tumors may be related to hormonal dependency of the neoplasm and to the eventual prognosis of the disease.

4720 STEROIDOGENESIS IN CEREBRAL METASTATIC CHORIONEPITHELIOMA TISSUE *IN VITRO*. (Eng.) Maeyama, M. (Kumamoto Univ. Medical Sch., Kumamoto, Japan); Ifuku, M.; Nakahara, K. *J. Endocrinol.* 65(3):425-428; 1975.

Steroidogenesis was investigated in homogenates of cerebral chorionepithelioma tissue incubated with [4-^{14}C]dehydroepiandrosterone (1,380 x 10^3 dpm), [7α-^{3}H]pregnenolone (3,070 x 10^3 dpm), or [1,2-^{3}H]-20α-hydroxypregn-4-en-3-one (1,860 x 10^3 dpm). Cerebral metastatic tissue from a chorionepithelioma was obtained from a patient in whom a latent period of 4 1/2 yr had elapsed between the removal of the primary tumor and the development of clinical metastases. The supernatant from 1.2 g tissue was incubated for two hours at 37 C with the above chemicals. The metabolites of dehydroepiandrosterone that were isolated and identified by thin-layer chromatography were androstenedione, testosterone, estrone, and estradiol; no estriol was detected. The only metabolite of pregnenolone and 20α-hydroxypregn-4-en-3-one isolated and identified was progesterone. No conversion of C-21 to C-19 steroids occurred in the metastatic chorionepithelioma tissue. The lack of estriol formation from dehydroepiandrosterone suggests that chorionepithelioma tissue lacks an enzyme for C-16 hydroxylation.

4721 MELANOMA CELLS RESISTANT TO INHIBITION OF GROWTH BY MELANOCYTE STIMULATING HORMONE. (Eng.) Pawelek, J. (Yale Univ. Sch. Med., New Haven Conn. 06510); Sansone, M.; Koch, N.; Christie, G.; Halaban, R.; Hendee, J.; Lerner, A. B.; Varga, J. M. *Proc. Natl. Acad. Sci. USA* 72(3):951-955; 1975.

Melanoma cells resistant to inhibition of growth by melanocyte stimulating hormone (MSH) were isolated and the relationships of cyclic AMP to the control of both the growth and melanization of these cells were determined. Cells from the Cloudman S91 mouse were cultured in a medium containing MSH (0.2 μM). Melanotic and amelanotic clones that grew in the presence of MSH were isolated and subcloned further to form clones *mel-1* and *amel-1*. The parental strain from which these lines were derived is designated PS1-wt (wild type). MSH or dibutyryl cyclic AMP (Bt_2AMP 250 μM) caused growth inhibition and morphological changes in wild-type cells but not in *amel-1* or *mel-1* cells. Wild-type cells had high basal tyrosinase activity which was stimulated further by MSH or Bt_2AMP; *amel-1* cells had very low basal tyrosinase activity which was not stimulated by MSH or Bt_2AMP. The *mel-1* cells also had very low basal tyrosinase activity but retained MSH or Bt_2AMP inducible activity. There was somewhat more MSH receptor activity in *amel-1* and *mel-1* cells than in wild-type cells. Bt_2AMP caused an increase in MSH receptor activity in *mel-1* and wild-type cells but

usually decreased the activity in *amel-1* cells. All three lines contained melanosomes. Endogenous cAMP levels, cAMP-dependent protein kinase activity, cAMP binding proteins, and cAMP transport were essentially the same for all three lines. Wild-type and *mel-1* cells showed increased intracellular cAMP levels in response to MSH and/or theophylline; *amel-1* cells did not. It is concluded that tyrosinase activity present in the absence of added MSH is related through a common biochemical pathway to MSH control of growth. However, MSH-inducible tyrosinase activity does not appear to be related to MSH control of growth. The morphological changes that occur following the addition of MSH or cAMP to melanoma cells are related to growth of the cells and not to melanization.

722 RELATIVE ABUNDANCE OF BIG AND LITTLE GASTRINS IN THE TUMOURS AND BLOOD OF PATIENTS ITH THE ZOLLINGER-ELLISON SYNDROME. (Eng.) Dockay, G. J. (VA Wadsworth Hosp. Center, Building 115 oom 115, Los Angeles, Calif. 90073): Walsh, J. H.; assaro, E., Jr. *Gut* 16(5):353-358; 1975.

he relative concentrations of big gastrin (G-34) nd little gastrin (G-17) were compared in the sera nd gastrinomas of Zollinger-Ellison syndrome pa- ients. Big and little gastrins were identified in ll ten serum samples and in all ten tumor biopsies xamined. In serum, G-34 was the major form of gas- rin and G-17 was a minor component; the mean re- ative abundance of G-17 (G17/[G17 + G34]) in serum as 0.18. In tumor, G-17 was the major component and -34 a minor component, and the relative proportions f G-17 and G-34 were 0.73 and 0.27 respectively. ollowing an iv injection of porcine secretin (2.0 ollowing an iv injection of procine secretion (2.0 /kg), there was a rapid increase in concentration f all forms of gastrin in the blood, but the in- rease in G-17 was proportionately greater than that f G-34. Differences in the half lives of G-17 and -34 may partly explain their relative abundancies n serum and tumor tissue.

723 AGING CHANGES IN CD-1 HaM/ICR MICE REARED UNDER STANDARD LABORATORY ONDITIONS. (Eng.) Homburger, F. (Bio-Res. onsult., Inc., Cambridge, Mass.); Russfield, B.; Weisburger, J. H.; Lim, S.; Chak, S. P.; eisburger, E. K. *J. Natl. Cancer Inst.* 55(1): -45; 1975.

determine the characteristics of an inbred use strain relevant to the planning of future xperiments in carcinogenesis, 300 CD-1 HaM/ICR ce were observed for two years, and necropsies re performed on 99 males and 102 females. rtality was 50% at 16 mo in the males and at 18 in the females. Among mice that came to autopsy, tal tumor incidence was 54% for males and 75% for males, with most neoplasms occurring after 18 mo. enomas or adenocarcinomas of the lung were the st frequent, followed by lymphoreticular tumors, scular tumors, hepatomas, subcutaneous fibro- rcomas, and adenocarcinomas of the mammary glands. Some degree of amyloidosis was seen in half the mice of both sexes, beginning at eight months in males and 12 months in females. Hyperplastic endometrium and myometrial changes seen in the old females suggested that this mouse stock might be useful in the investigation of spontaneous reproductive pathology. The many spontaneous tumors found in the mice (most of them occurring after 18 mo) made the detection of weak carcinogens difficult in a two-year experiment. Variability in tumor incidence among small groups of mice emphasized the need for adequate samples.

4724 PLACENTAL TRANSFER OF TRITIUM-LABELED PROSTAGLANDIN A_1 IN THE RAT. (Eng.) Persaud, T. V. N. (Dept. Anatomy, Univ. Manitoba, Winnipeg, Manitoba, Canada R 3E OW3); Jackson, C. W. *Exp. Pathol. (Jena)* 10(5/6):353-358; 1975.

The placental transfer and tissue distribution of [^{3}H]-prostaglandin A_1 (^{3}H-PGA$_1$) were studied in pregnant Long Evans rats. When ^{3}H-PGA, (25 μCi iv) was given on the 21st gestational day, significant levels were found in the fetal gut, kidney, and brain, within five min. Subsequently these levels increased or remained constant. In rats injected on day 18, the dpm/min/mg wet wt in the amniotic fluid increased from 8,520 at five min, to 58,600 at 24 hr. It appears that PGA, acts directly on the conceptus.

4725 PROPERTIES OF THE GENOME IN NORMAL AND SV40 TRANSFORMED WI38 HUMAN DIPLOID FIBROBLASTS. II. METABOLISM AND BINDING OF HISTONES. (Eng.) Krause, M. O. (Dept. Biochemistry, Univ. Florida, Gainesville, Fla. 32610); Stein, G. S.* *Exp. Cell Res.* 92(1):175-190; 1975.

The composition, metabolism and binding of the histone fractions from normal and simian virus 40 (SV40)-transformed WI38 human diploid fibroblasts were compared. The fibroblasts were grown in monolayer culture in Eagle's basal medium containing 10% fetal calf serum. Metabolism of histones was determined by labeling cells either with a mixture of ^{3}H-arginine and ^{3}H-lysine and ^{32}P or with ^{3}H-acetate. Two alternate procedures were used for nuclear isolation. The first method involved lysis of cells by treatment with 80 mM NaCl, 20 mM EDTA, and 1% Triton X-100 at pH 7.2. Under these conditions, (F1, F3, F2b, and F2a1) all five histone fractions were retained in the isolated nuclei. The second method involved lysis of cells at pH 2.4 with 10 mM Mg^{2+}, 10 mM Ca^{2+}, 25 mM citric acid, 0.1 M sucrose and 0.1% Triton X-100. This method resulted in optimal recovery of arginine-rich histones F3 and F2a1. Histones were extracted from the nuclei of both normal and transformed cells at 4C with 0.25 M HCl and were fractionated by polyacrylamide gel electrophoresis. While the relative amount of each histone fraction was similar in normal and SV40-transformed cells, substantial increases in the levels of F3 acetylation and F1 (lysine rich)

and F2a2 phosphorylation were observed for the histones of the transformed cells. Differences in extractability of arginine-rich histones with 0.25 M HCl were also observed. F3 was extracted more rapidly than F2a1 from nuclei of normal WI38 fibroblasts, but the reverse was true in the transformed cells. The extractability of histones may reflect the tightness with which the histone molecules are associated with one another and with the other components of the chromatin complex. Differences in histone binding may be mediated at several levels; modifications in the histones themselves may result in conformation changes which are likely to alter intermolecular associations. It is also possible that the nonhistone chromosomal proteins associated with the genome of SV40-transformed cells may be responsible for viral-induced variations in histone binding. It is not clear whether modifications in histone binding are functionally relevant to the altered biological properties associated with viral transformation, but previously published evidence suggests that the binding of histones to DNA may be instrumental in dictating transcriptional properties of the genome.

4726 INCREASED AMIDOPHOSPHORIBOSYLTRANSFERASE (AT) ACTIVITY IN HEPATOMAS [abstract]. (Eng.) Weber, G. (Indiana Univ. Sch. Med., Indianapolis, Ind.); Prajda, N. *Proc. Am. Assoc. Cancer Res.* 16:50; 1975.

4727 NEUTROPHIL ALKALINE PHOSPHATASE: COMPARISON OF ENZYMES FROM NORMAL SUBJECTS AND PATIENTS WITH POLYCYTHEMIA VERA AND CHRONIC MYELOGENOUS LEUKEMIA. (Eng.) Rosenblum, D. (Washington Univ. Sch. Med., St. Louis, Mo.); Petzold, S. J. *Blood* 45(3):335-343; 1975.

4728 HUMAN TUMOR NON-REGAN ALKALINE PHOSPHATASE ISOENZYME [abstract]. (Eng.) Fishman, W. H. (Tufts Cancer Res. Cent., Boston, Mass.); Driscoll, S.; Miyayama, H.; Fishman, L. *Proc. Am. Assoc. Cancer Res.* 16:195; 1975.

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